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SYMPOSIUM
Glomerulonephritis

Special Editors
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INTRODUCTORY STATEMENT TO SYMPOSIUM ON GLOMERULONEPHRITIS

THE papers which comprise this symposium on glomerulonephritis attest to the student's need for familiarity with many different disciplines of medicine. Indeed, a detailed study of all the facets of glomerulonephritis offers a liberal education in internal medicine, with detours into the basic fields upon which progress in internal medicine depends.

There have been significant advances in our knowledge of glomerulonephritis in the past two decades. These consist of an increase in pathologic, bacteriologic, and immunologic information, new diagnostic techniques, improvement in methods of renal functional measurements, and some therapeutic advances. Such contributions should temper the frequent and rather apologetic statement that little more is known today about nephritis than was so ably presented more than a century ago in Richard Bright's papers.

Nevertheless, many defects and gaps in our knowledge are still obvious. Indeed, considerable disagreement enlivens current discussions concerning the classification and relationship of several important features of Bright's disease. The most outstanding example of controversy is the difference of opinion relative

to the place where the nephrotic syndrome fits into the natural history of glomerulonephritis. Some investigators believe that true or lipoid nephrosis, especially in children, is a specific disease with an etiology distinct from that of classic diffuse glomerulonephritis. At least, no relationship between Group A hemolytic streptococcal infection and the development of nephrosis has yet been demonstrated. Others contend that the nephrotic syndrome of adults represents a phase of diffuse glomerulonephritis. Finally, there are those who subscribe to the belief that a combination of both views is correct. Even pathologists disagree on their interpretations of renal histology in relation to this problem.

Another area where available data do not yet permit a definitive viewpoint has to do with the mechanism of production of classic acute diffuse glomerulonephritis. Practically all students of the disease now agree that the majority of instances of acute glomerulonephritis are associated with Group A hemolytic streptococcal infections and that the disease does not result from bacteriologic invasion of the kidneys. However, the mechanism of development of the glomerular lesion is not known. At least two major possibilities exist, an antigen-antibody reaction somehow set off by Group A hemolytic streptococci, or a direct toxic effect by the products of this organism.

On a clinical level, the pathogenesis of the edema of acute glomerulonephritis is not settled to the satisfaction of all workers. Some evidence has been advanced to support the concept that this edema is the result of increased capillary permeability, of renal retention of fluid and electrolyte, or of congestive heart failure. The final solution of this problem is of more than academic importance, since rational therapy must be based on knowledge of the pathologic process.

The subjects and authors of this symposium were selected to provide the reader with the current thought and techniques applied by students of glomerulonephritis to the pathogenesis, diagnosis, and management of the disease. The first paper is designed to furnish a definition of terms, to keep unnecessary disagreements at a minimum, and, finally, to present a general concept of the natural history of glomerulonephritis which, it is hoped, will delimit the scope of the problems to be discussed and furnish a framework of reference for the papers of this symposium.

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NATURAL HISTORY OF GLOMERULONEPHRITIS

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THE nephron can react to different noxious agents in only a limited manner. As a result, the pathologist is likely to lump together a number of diseases of quite different etiologies under the single diagnosis of glomerulonephritis. Furthermore, advancing renal disease so distorts the architecture of the kidney that initial and perhaps more specific and distinctive changes are obscured. Chronic renal disease is frequently complicated by hypertension, which can impose additional secondary changes on the kidneys. As a result, the clinician is sometimes in a better position than the pathologist to arrive at the proper interpretation of a renal disease. However, the clinician's task is often difficult because of the limitations in knowledge outlined in the "Introductory Statement." Perhaps the newly developed technique of percutaneous renal biopsy[1-3] will be a stimulus for joint studies of the natural history of glomerulonephritis by the pathologist and the clinician. The anatomic lesions of glomerulonephritis will be considered in detail in subsequent papers of this symposium.

Despite obvious obstacles, some kind of concept of the natural history of glomerulonephritis is necessary for an orderly consideration of the disease. A schema outlining the authors' concept is presented in Fig. 1. This schema is similar in some respects to those of other workers and is subject to modifications as knowledge accumulates. Time is indicated by the abscissa of the figure, while that status of the kidneys is shown by the ordinate, 100 per cent indicating normal kidneys. The degree of kidney disease represented by various percentages less than 100 is not intended to be quantitatively precise, nor is the time factor meant to be absolute. Reference to this figure from time to time may assist the reader in the subsequent discussions.

ACUTE GLOMERULONEPHRITIS

The initial acute attack is the simplest aspect of glomerulonephritis to consider. Dark, red, or smoky urine, along with the characteristic edema occurring one to four weeks after an infection, are the important symptoms that cause the patient (or his parents) to seek medical advice. Proteinuria, hematuria, cylindruria (particularly cellular casts), hypertension, or nitrogen retention aid in

establishing the diagnosis in a patient who has no history of previous renal disease. Other aspects of the clinical picture and laboratory findings will be discussed in subsequent papers of this symposium.

Many years ago, Richard Bright[4] realized that glomerulonephritis was frequently associated with upper respiratory tract infections. More recently, numerous laboratories have collected considerable bacteriologic and immunologic evidence to show that the majority of instances of classical acute diffuse glomerulonephritis follow Group A hemolytic streptococcal infections,[5,6] and further, that several specific types of streptococci (notably Type 12) are particularly nephritogenic.[7,8]

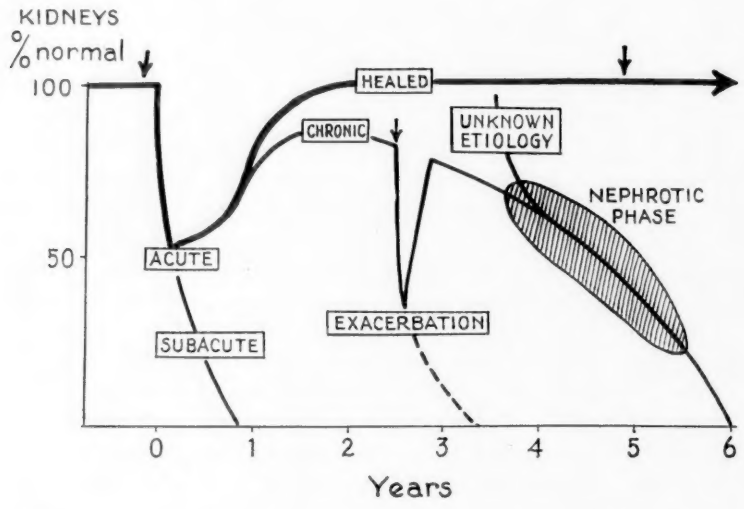

Fig. 1.—Natural history of diffuse glomerulonephritis. Time is indicated by the abscissa of the figure, while the status of the kidneys is shown by the ordinate, 100 per cent indicating normal kidneys. The degree of kidney disease represented by various percentages less than 100 is not intended to be quantitatively precise, nor is the time factor meant to be absolute. The arrows indicate Group A hemolytic streptococcal infections. The dashed line below exacerbation indicates that a small number of exacerbations are followed by rapid progression of renal functional impairment, perhaps analogous to the relatively uncommon subacute course subsequent to an initial attack of acute glomerulonephritis. (Courtesy *Disease a Month*, The Year Book Publishers, Chicago, Ill.)

Most workers believe that acute glomerulonephritis is an expression of an antigen-antibody reaction, since hemolytic streptococci are not found in the kidneys of individuals in any stage of glomerulonephritis. This thought is strengthened by the latent period of one to four weeks between the infection and the onset of nephritis and by several immunologic considerations. However, the possibility of a nephritogenic factor associated with specific strains of streptococci has not yet been ruled out.

Certain biologic considerations suggest that host differences as well as characteristics of the hemolytic streptococcus may be of significance in the pathogenesis of glomerulonephritis and rheumatic fever. These diseases are generally considered to be related to Group A hemolytic streptococcal infections, but a number

of biologic differences exist between them.[9,10] These are listed in Table I. The bacteriologic and immunologic aspects of glomerulonephritis will receive consideration in subsequent papers of this symposium.

TABLE I. BIOLOGIC DIFFERENCES BETWEEN GLOMERULONEPHRITIS AND RHEUMATIC FEVER

BIOLOGIC FEATURE	GLOMERULONEPHRITIS	RHEUMATIC FEVER
Geographical distribution	Uniform	More common in Northern latitudes
Age	Any age	Rare in infancy
Familial factors	Family contacts	Familial tendency
Sex incidence	Males predominate 2 to 1	Equal
Second attacks	Rare	Common
Average latent period between infection and first attack	10 days	18 days
Latent period between infection and exacerbation	Shortened as compared to latent period in first attack	Same as latent period in first attack
Relation of degree of ASL* increase to incidence of first attacks	No relation	Incidence of attacks proportional to degree of ASL increase
Time of ASL increase in relation to onset of relapse	After	Before
Serum complement	Decreased	Increased
Type of initiating Group A hemolytic streptococcus	4, 12, 18, 25, and untyped (12 predominates)	Any type

*ASL = Antistreptolysin O titer.

Although the majority of instances of acute diffuse glomerulonephritis are associated with Group A hemolytic streptococcal infections, infections due to other organisms also have been incriminated. A number of instances of diffuse glomerulonephritis have developed during the course of subacute bacterial endocarditis. Acute nephritis has also been described following pneumococcus pneumonia and following malaria. Numerous other organisms have been stated to produce nephritis, but generally the evidence has been incomplete or not convincing. Although the clinical picture and other aspects of acute glomerulonephritis following subacute bacterial endocarditis or pneumococcus pneumonia are similar in many respects to the disease associated with Group A hemolytic streptococcal infections, this discussion will be limited to the latter.

Discrete renal functions as measured by the clearance techniques demonstrate a characteristic pattern of dysfunction[11-13] which reflects the anatomic changes of acute glomerulonephritis. Any consideration of renal function in disease should be made in the light of anatomic alterations in the nephrons, especially as revealed by Oliver's classic work on dissections of nephrons in disease.[14]

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As would be expected, the glomerular filtration rate is reduced more than any other kidney function in acute glomerulonephritis. Renal blood flow also may be reduced in severely ill patients, but frequently it is in the normal range. Typically, therefore, the filtration fraction (ratio of glomerular filtration rate to renal plasma flow) is reduced in acute glomerulonephritis. Function of the proximal renal tubules as measured by the maximal excretory capacity for p-aminohippuric acid (Tm PAH) or maximal reabsorptive capacity for glucose (Tm glucose) also may be reduced. However, in the milder forms of the disease, renal blood flow: Tm ratios greater than normal indicate relative renal hyperemia. Concentrating ability of the kidneys is generally not impaired during the first few days of the initial acute attack. Thereafter, however, the specific gravity may be fixed at or near 1.010 for many weeks or even months.

These characteristic renal functional disturbances persist despite circumstances that are ordinarily associated with quite different patterns of dysfunction. Both congestive heart failure[15] and primary or malignant hypertension[16] are ordinarily associated with greater reductions of renal plasma flow than of filtration rate and hence are characterized by an increased filtration fraction. However, when acute nephritis is associated with hypertension or congestive heart failure, the filtration fraction remains decreased or at least within the normal range.[12]

These tests of specific renal functions can be of diagnostic aid. Patients with hypertensive arteriolar nephrosclerosis may exhibit urinary abnormalities similar to those of acute glomerulonephritis. When, in addition, the hypertensive patient has congestive heart failure, the clinical picture may be confused with that of acute nephritis. At times, congestive heart failure alone, when associated with heavy proteinuria, also may be confused with acute nephritis. Further, acute nephritis may cause congestion of the circulation and, occasionally, congestive heart failure (vide infra). The clinical picture may be so dominated by the circulatory manifestations that its renal origin is overlooked. In Table II, typical effects of these different disorders on renal functions are compared with those of acute glomerulonephritis.

TABLE II. TYPICAL RENAL FUNCTION ALTERATIONS IN ACUTE GLOMERULONEPHRITIS, PRIMARY HYPERTENSIVE DISEASE, AND CONGESTIVE HEART FAILURE

	ACUTE GLOMERULONEPHRITIS	PRIMARY HYPERTENSIVE DISEASE	CONGESTIVE HEART FAILURE
Glomerular filtration rate (GFR)	Decreased	Normal or slightly decreased	Decreased
Renal plasma flow (RPF)	Increased, normal, or slightly decreased	Decreased	Greatly decreased
Filtration fraction (GFR/RPF)	Decreased	Increased	Greatly increased
Maximum excretory capacity for PAH (Tm_{PAH})	Decreased	Decreased	Normal or decreased
GFR/Tm_{PAH}	Decreased	Increased	Decreased
RPF/Tm_{PAH}	Increased	Decreased	Decreased

Some of the simpler measures of renal function are of considerable value in defining the physiologic derangement, especially if interpreted in the light of their relations to the more specific measurements. The urea and creatinine clearances, for instance, are more a reflection of glomerular filtration rate than of any other renal functions. The urea clearance, however, is less than the filtration rate by virtue of passive back-diffusion of some of the filtered urea across the tubules. The urea clearance, furthermore, varies directly with the urine flow. Some creatinine is excreted by the renal tubules of man and hence its clearance is greater than glomerular filtration. Likewise, phenolsulfonphthalein (PSP) excretion is a crude measure of renal plasma flow. Phenolsulfonphthalein is removed so rapidly by the renal tubules from the blood flowing through the kidneys that its excretion rate is dependent upon its rate of delivery to the kidneys. However, as renal disease progresses and the ability of the renal tubule cells to extract PSP becomes impaired, its excretion rate becomes more a reflection of decreased tubular function than of renal blood flow.

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Edema is a common manifestation of acute glomerulonephritis. Disagreement exists as to its pathogenesis. Many investigators believe that the edema of acute glomerulonephritis is due to congestive heart failure. This is based on the belief that acute hypertension leads to myocardial insufficiency or that definite myocardial damage occurs in acute glomerulonephritis. Either one or both of these mechanisms are then assumed to be responsible for the congestive heart failure. Proponents of this hypothesis point to the fact that the heart may be enlarged, that pulmonary edema is common, that venous pressure may be increased, and that the liver may be enlarged.[17] However, several facts weaken this argument. The cardiac output is rarely decreased in acute glomerulonephritis[18] and the circulation time is normal or rapid. Such findings are not compatible with ordinary low cardiac output congestive heart failure. Rather, they may reflect congestion of the circulation due to salt and water retention in the presence of a normal heart. A similar clinical state is seen in the acute renal failure due to carbon tetrachloride poisoning where the administration of excessive amounts of fluid produces identical physiologic abnormalities. Another line of evidence which suggests a mechanism for the edema formation in acute glomerulonephritis other than congestive heart failure is furnished by the recent finding that less sodium in relation to total body water is retained by patients with acute glomerulonephritis than by patients with edema due to congestive heart failure.[19]

It has been suggested that generalized capillary damage may account for the edema in acute nephritis. This belief has been based chiefly on the localization of edema about the face and eyes, on the occurrence of edema and hypertension prior to or even without urinary abnormalities, and on the early observations that the edema fluid of acute glomerulonephritis contains relatively large amounts of protein. However, localization of edema in the tissues of the face is not surprising in patients with fluid retention who are confined to bed and who do not have a local or general increase of venous pressure. Likewise, the most recent studies[20] of edema fluid in acute nephritis reveal a protein content characteristic of transudates rather than of inflammatory reactions or of generalized capillary

damage. Extensive generalized capillary damage should lead to considerable loss of protein and fluid from the vascular system, resulting in an increased hematocrit. The usual observation in acute nephritis, however, is a decrease in hematocrit with a subsequent return to normal following diuresis.

The considerations just presented suggest that more emphasis should be placed upon a renal mechanism to account for the fluid and salt retention in acute nephritis. The observed reduction of filtration rate may well play some role in the pathogenesis of nephritic edema, especially in patients whose filtration rates are rapidly and suddenly reduced. However, some patients with massive edema have been shown to have normal glomerular filtration rates.[12] Furthermore, the urea clearance in acute glomerulonephritis is frequently reduced out of proportion to the filtration rate and the degree of oliguria. Since reabsorption of urea by the renal tubules appears to represent passive diffusion, a possible explanation for the low urea/inulin clearance ratio in most instances of acute glomerulonephritis could be renal epithelial cell damage. In any case, data have been accumulated to indicate that diuresis during recovery from an episode of acute nephritis can take place without any increase in glomerular filtration rate or renal blood flow.

Acute glomerulonephritis can occur in all degrees of severity. Mortality in most series is reported to be approximately 5 per cent, with death usually being due to anuria or severe oliguria associated with hyperkalemia, convulsions, or acute pulmonary edema. In some other instances, the disease may be so mild as to produce no symptoms and is detected only by frequent and careful examinations of the urine for four weeks following the hemolytic streptococcal infection. When such serial examinations are made, a high incidence of transient and slight proteinuria and hematuria is encountered.[21] These abnormalities most commonly occur a few days after the streptococcal infection and probably do not represent acute diffuse glomerulonephritis. Likewise, the small but definite proteinuria and hematuria noted by Lyttle,[22] who did serial Addis counts two to four weeks after the onset of scarlet fever, is probably of doubtful clinical significance.

Nevertheless, some instances of mild and transitory urinary abnormality, occurring one to four weeks after Group A hemolytic streptococcal infections, undoubtedly represent attacks of acute diffuse glomerulonephritis. This view is strengthened if transitory hypertension and/or edema also appears. Such mild attacks frequently escape detection, yet are of considerable importance. Many patients with chronic diffuse glomerulonephritis give no history suggestive of an earlier attack of acute glomerulonephritis. Some students of the disease believe that most instances of chronic glomerulonephritis represent the residua of a very mild and undetected attack of acute glomerulonephritis which failed to heal. With slow progression of the disease, the patient's chronic glomerulonephritis is detected by routine urinalysis or by the eventual development of the signs and symptoms of renal failure. However, with the present state of knowledge and available techniques, this hypothesis cannot be proved definitely and the alternative possibility remains that many or most instances of chronic diffuse glomerulonephritis without evidence of antecedent acute nephritis represent a disease or diseases of different and unknown etiologies.

The prognosis of acute glomerulonephritis is excellent. As stated earlier, the immediate mortality is generally less than 5 per cent. An occasional patient

may pursue a rapidly progressive subacute course characterized by continued urinary abnormalities and decreasing renal function. Death in these patients usually occurs within six to twelve months of the onset of the acute episode. Patients in this phase usually exhibit moderate proteinuria, microscopic hematuria, may or may not have hypertension, and frequently have evidence of some of the elements of the nephrotic phase. Pathologically, epithelial crescents are frequently encountered at autopsy in subacute glomerulonephritis. Unfortunately, however, evidence of a good correlation between the clinical and pathologic concepts concerning subacute nephritis has not yet been published. After several days or weeks, the majority of patients with acute glomerulonephritis begin to improve rapidly. As they lose edema and hypertension, proteinuria and hematuria decrease and soon most of the measurements of renal function also approach normal. Healing may be considered to have occurred when proteinuria has permanently ceased. Microscopic hematuria and impaired concentrating ability persisting for many months after proteinuria has disappeared are not incompatible with healing.

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HEALED ACUTE GLOMERULONEPHRITIS

Some disagreement exists concerning the incidence of permanent healing following acute glomerulonephritis. Most estimates today range between 85 and 95 per cent. Unfortunately, techniques which allow a decision as to whether the process will heal or progress are not available at the onset of the disease. Proteinuria will clear within six months in the majority of patients whose disease eventually heals. If the protein persists for eighteen months or longer, the diagnosis of chronic nephritis is established. The propensity for healing of acute glomerulonephritis does not appear to be correlated with the severity of the initial process. Indeed, some authors have commented that the most explosive types of acute nephritis usually heal completely.[23] Likewise, no correlation appears to exist between the persistence of the offending Group A hemolytic streptococcus and the outcome of the acute glomerulonephritic process.

The patient in whom acute glomerulonephritis has healed is in a relatively strategic position since second attacks are extremely rare, even when the patient undergoes subsequent Group A hemolytic streptococcal infections.[24] The reason for the infrequency of second attacks of acute glomerulonephritis is not definitely known, although the rarity of infection with a second nephritogenic strain of hemolytic streptococci seems more reasonable than a true refractory state.

CHRONIC GLOMERULONEPHRITIS

Throughout the early course of chronic glomerulonephritis, the only evidence of the disease detectable by ordinary clinical examinations may be proteinuria. Hypertension is rare at this time. Simple measures of renal function frequently are normal or only questionably reduced, although the precise measures of renal functions may reveal a decreased glomerular filtration rate and sometimes a decreased filtration fraction. This form of chronic glomerulonephritis is frequently called the latent phase. The duration of chronic glomerulonephritis is extremely variable, sometimes lasting for thirty years or longer. Eventually,

however, renal functional impairment becomes evident and the patient succumbs to his disease, barring previous death from an unrelated process. The factors concerned with the rate of progress of chronic glomerulonephritis are unknown. It has not yet been demonstrated that persistent or repeated Group A hemolytic streptococcal infections play a significant role in the progression of chronic glomerulonephritis, but this possibility cannot be excluded. The clinical course, renal functional changes, and other important features of chronic glomerulonephritis will be considered in several papers in this symposium.

THE EXACERBATION IN CHRONIC GLOMERULONEPHRITIS

The course of chronic glomerulonephritis may be complicated by several different types of episodes. The exacerbation in chronic glomerulonephritis is considered to be a replica of the initial acute attack. However, the interval between infection and the acute episode is a matter of days in the case of the exacerbation instead of weeks in the initial attack.[9] Since many of the characteristic features of the initial acute attack such as proteinuria, hypertension, edema, and decreased renal function already may be present, the diagnosis of the exacerbation is at times quite difficult. After considerable deliberation, Seegal and his colleagues[25] recommended that the arbitrary criterion for an exacerbation in chronic glomerulonephritis be an abrupt and significant increase in the degree of hematuria. So defined, some 70 per cent of exacerbations are associated with Group A hemolytic streptococcal infections. The remainder of the exacerbations are associated with infections of other etiologies.

As previously discussed, the initial attack of acute glomerulonephritis generally is associated with infections due chiefly to a few "nephritogenic" strains of Group A hemolytic streptococci. Adequate immunity presumably is developed against subsequent infections due to the same strain. Therefore, the reason why some individuals with chronic glomerulonephritis may undergo as many as five exacerbations is difficult to understand. Further, it is difficult to see why so many exacerbations are associated with Group A hemolytic streptococcal infections if the exacerbation represents a nonspecific reaction to infection.

Differentiation between the exacerbation and the initial acute attack is sometimes difficult if the prior history of the patient is unknown. A useful diagnostic point in this situation is the length of time between the onset of the infection and the onset of the bout of nephritis. This is only a day or so in the exacerbation, in contrast to several weeks for the initial attack. The above definition of the exacerbation, of course, excludes the development of the nephrotic syndrome, rapid progression of renal functional impairment, sudden appearance of hypertension, and the development of congestive heart failure as evidences for an exacerbation unless these states are associated with an increased hematuria.

Probably no more than 20 per cent of patients with chronic glomerulonephritis develop exacerbations.[25] Contrary to common belief, the exacerbation rarely appears to accelerate the rate of progression of the underlying chronic process. Using simple clinical measures of kidney function, the renal status of

the majority of patients with exacerbations is found to return to pre-exacerbation levels. The possibility is not excluded, however, that some nephrons have been damaged permanently during the exacerbation.

THE NEPHROTIC SYNDROME

The nephrotic syndrome, defined as massive edema, heavy proteinuria, hypoalbuminemia, and hypercholesterolemia, is observed in approximately one-half the patients who are eventually diagnosed by the pathologist as having chronic glomerulonephritis.[26]

The nephrotic syndrome has been seen during the course of chronic glomerulonephritis known to have followed a proved attack of acute nephritis associated with Group A hemolytic streptococcal infection. Well-documented instances of this sequence of events, however, are rare and the possibility exists that a different, unknown agent or mechanism is responsible for the majority of cases of the nephrotic syndrome in chronic glomerulonephritis. Many workers believe that its pathogenesis is related to an unspecified antigen-antibody reaction. Since the loss of large amounts of serum albumin into the urine is the basis for the development of the nephrotic syndrome, glomerular damage due to any cause that permits sufficient protein loss could account for the syndrome. Hence, it is not surprising that the nephrotic syndrome can occur in a variety of diseases such as systemic lupus erythematosus, renal amyloidosis, the Kimmelstiel-Wilson syndrome, renal vein thrombosis, following certain drugs such as dilantin, following bee stings, poison oak sensitivity, and in true lipoid nephrosis. It is believed that the damage to the glomerular basement membrane in the nephrotic syndrome may result from mechanical, hyperergic, or unknown causes.

Most instances of the nephrotic syndrome in adults develop with little or no hematuria, without hypertension, and without obvious impairment of renal function. This insidiously developing nephritis has been termed type B nephritis by Longcope[27] and type II nephritis by Ellis[28] and is to be contrasted with the acute hemorrhagic glomerulonephritis typically associated with Group A hemolytic streptococcal infections, designated by these authors as type A and type I nephritis, respectively. Subsequent papers of this symposium will consider the nephrotic syndrome in detail.

TERMINAL GLOMERULONEPHRITIS

As chronic glomerulonephritis progresses toward the terminal stage, the patient becomes listless, weak, and pale. Anemia usually does not become marked until nitrogen retention is well established.

At this stage, tubular function undergoes more rapid impairment than the glomerular filtration rate. This is indicated by increasing loss of PSP excretory function and of concentrating ability, and by increasing filtration rate to Tm ratios.

The absolute loss of renal functional tissue is responsible for the reduced ability of the kidneys to form ammonia and hence to combat acidosis, and also contributes to the retention of inorganic and organic anions that may lead to

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acidosis. The distortion between the glomerular and tubular functions, moreover, may lead to a variety of water and electrolyte abnormalities. Thus, glomerular damage out of proportion to the impairment of tubular function predisposes to the retention of water and electrolyte. This may be the situation in acute episodes either in the initial attack or in the exacerbation. The opposite combination, however, would lead to the demineralization or loss of electrolytes and fluid which is common in the later stages of the disease. A reversal in the filtration rate: Tm ratio frequently occurs in patients with chronic nephritis at just about the time the nephrotic syndrome disappears. This transition heralds the onset of the terminal phase of the disease, which may be characterized by water and salt depletion.

Although marked impairment of renal function ordinarily leads one to suspect that a patient may be threatened with hyperkalemia, hypokalemia is, in fact, more common in the terminal phases of chronic renal disease.[29] Despite marked impairment of glomerular filtration rate, excessive amounts of potassium may be lost in the urine or, more commonly, in vomitus. The "salt-losing nephritis" is in some instances probably due to inability of the distal tubules to form adequate amounts of base-sparing ammonia and in others to some unspecified glomerular-tubular imbalance.

The course of events in the terminal phases of chronic glomerulonephritis is extremely variable and depends upon such factors as electrolyte changes, congestive heart failure, the presence of infection, vomiting, and the degree of anemia. The worsening uremic state, convulsions, tetany, colitis, and pericarditis are ominous manifestations.

A detailed discussion of many of the features of glomerulonephritis touched on in this resumé of its natural history will be presented in the articles which follow.

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GLOMERULAR NEPHRITIS AND LIPID NEPHROSIS: IDENTITIES AND MECHANISMS

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DURING the nineteenth century, Bright's disease, or nephritis, was subdivided on clinical grounds into acute, chronic parenchymatous, and chronic interstitial nephritis. Chronic parenchymatous nephritis was recognized by the presence of proteinuria and edema; chronic interstitial nephritis by hypertension and cardiac hypertrophy. This clinical era of interpretation of Bright's disease lasted until the turn of the century. It was followed by the present pathogenetic era.*

The pathogenetic concept of Bright's disease was introduced in 1905 at a joint session of clinicians and pathologists by the famous clinician von Müller,[50] who recommended strict distinction between degenerative and inflammatory diseases of the kidneys and suggested that the term nephrosis be used in all cases which are purely degenerative in character, or in which there is doubt about the inflammatory nature. We owe the ready acceptance of this concept largely to the publication in 1914 by Volhard and Fahr[59] of their monograph which marked "one of the great milestones in the knowledge of this field."[26] But credit is due also to Van Slyke and his associates[56] and to Addis and Oliver,[1] who strengthened this concept through quantitative chemical and functional studies and through the introduction of quantitative urinalysis. It is noteworthy that the new contributions were all fruits of clinicopathologic cooperation.

At the meeting in 1905, where von Müller made his notable contribution, Volhard[57] recommended an anatomic classification, namely, a distinction between "glomerular and tubular nephritides." Recently, another attempt has been made to introduce such a classification.[2] A pathogenetic classification of renal disease "of necessity includes a large anatomic (and functional) element,"[26] since renal disease is conditioned by renal function, and this rests on renal structure. A primarily anatomic classification, however, serves no useful purpose. Even Volhard did not accept his own recommendation. Instead, he became one of the outstanding exponents of the pathogenetic view.[59]

*The term pathogenesis refers to the morbid processes or mechanisms which determine the nature of a disease and hence its signs and symptoms; it must not be confused with etiology, which pertains to the cause of a disease. As one and the same agent may induce a variety of diseases, and as many diseases are etiologically obscure, modern classification of disease is based on pathogenetic rather than etiologic grounds. This should be kept in mind when identification of a given disease is attempted.

Although most students of Bright's disease now distinguish between inflammatory, degenerative, and neoplastic renal diseases and hence use such terms as nephritis and nephrosis, frequently no distinction is made between the nature of these diseases and the disturbances in function with which they are associated. Thus, some observers mean the nephrotic syndrome when they speak of nephrosis, while others mistake renal failure for glomerular nephritis. As this has caused much confusion in this field, this review will begin with a discussion of the differences between these entities.

THE NEPHROTIC SYNDROME

While nephrosis is a name of a group of diseases, the term nephrotic syndrome refers to a distrubance in function, namely, to proteinuria followed by hypoproteinemia and edema and associated frequently with hyperlipemia. While there are many nephroses (see below), there is only one nephrotic syndrome.

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The genesis of the nephrotic syndrome has long been a mystery. Volhard and Fahr,[59] in 1914, and Munk,[51] in 1918, believed that it was tubular in origin. In fact, these authors went so far as to claim that the amyloidosis of the glomeruli in amyloid nephrosis had nothing to do with the proteinuria in this disease, apparently because in lipid nephrosis the glomeruli were believed to be essentially normal, while the tubules showed the same degeneration in both diseases.

In 1925, Fahr[25] agreed that the glomerular changes in both amyloid and lipid nephrosis were possibly of much greater importance than thought at first. He now felt that both these diseases were "glomerular nephroses" as well as "tubular nephroses," and that the glomerular changes were the reason why these diseases could terminate in contracted kidneys. However, he did not trace the proteinuria to the glomerular changes. He still thought that this was tubular in origin.

The first who claimed that the nephrotic syndrome was due to an alteration of the glomeruli were Löhlein,[37-41] Schlayer,[54] and Addis,[1] but it remained for Bell[8] to relate the proteinuria of lipid nephrosis to the glomerular changes first observed by Fahr.[25,59] Bell's demonstration of thickening of the filtering membrane in lipid nephrosis was accomplished through application of a trichrome stain. However, in 18 of his 55 cases the membrane appeared to be normal; 15 of these individuals were under ten years of age.[9] In 1951, we[19] showed that thickening of the filtering membrane of the glomeruli can be demonstrated in all cases of lipid nephrosis in children, adults, and experimental animals if Ritter and Oleson's[53] combined Hale and Hotchkiss-McManus procedure is employed.* Bell's and our observations are at variance with the recent contention of Allen[3] that the recognition of this lesion does not require any more elaborate technique than a routine stain with hematoxylin and eosin.

Today, it is apparent that the nephrotic syndrome occurs only in diseases that cause widespread alteration of glomeruli. Hence, it is seen in chronic diffuse hemorrhagic glomerulonephritis and in the various glomerulonephroses,

*This observation refers to whole kidneys. Needle biopsies may fail to show the lesion because of its focal distribution. Recent electron microscopic studies by Goodman, Modern, and Piel, which are being published in the *Journal of Experimental Medicine*, seem to show that the swelling of the filtering membrane affects all its layers.

Fig. 1.—Thickening of filtering membrane in lipid nephrosis (*A*), amyloid nephrosis (*B*), lupus nephrosis (*C*), and chronic glomerular nephritis (*D*). Patients A and B suffered from the nephrotic syndrome without evidence of renal failure. Patients C and D died in uremia; they did not have the nephrotic syndrome.

but not in the tubular nephroses (see below). The glomerular alteration has been demonstrated clinically as well as histologically.[14] The morphology of the alteration varies with the nature of the glomerular disease.[2,19,55] In amyloid, lipid, and lupus nephrosis it is characterized by thickening (swelling) of the filtering membrane (Fig. 1, *A* and *B*). If the thickened membrane is hyalinized, as in wire-looping in lupus erythematosus disseminatus (Fig. 1, *C*) or in certain cases of chronic diffuse hemorrhagic glomerular nephritis (Fig. 1, *D*), however, the predominant functional disturbance may be that of renal failure rather than of proteinuria.

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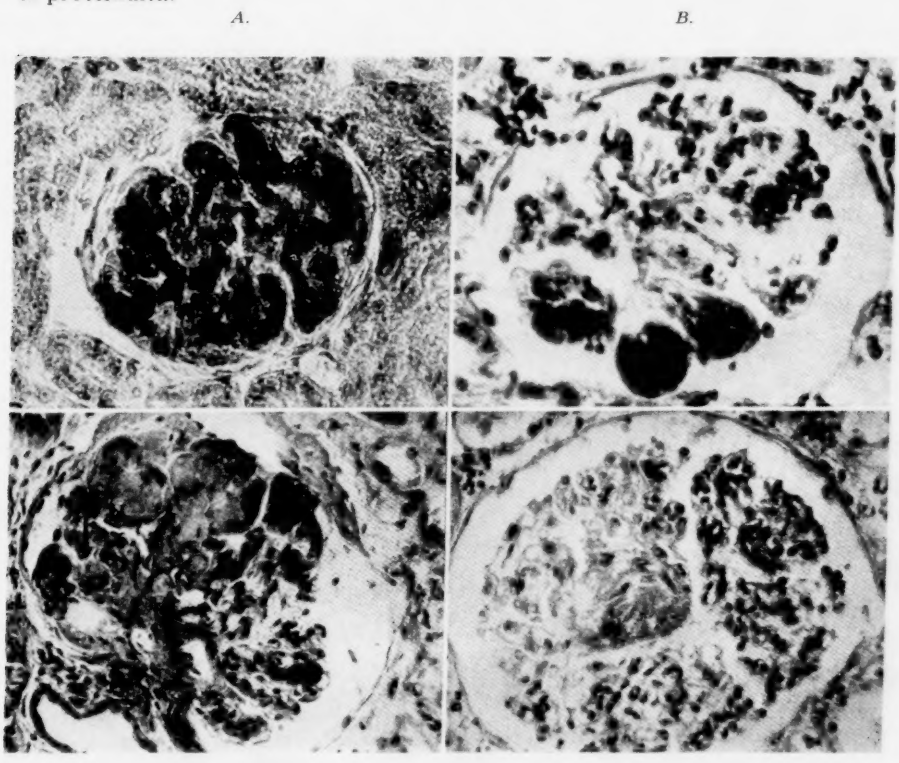

Fig. 2.—Thrombosis of capillary loops in experimental lipid nephrosis in a rat (*A*), in lupus nephrosis (*B*), and in diabetic glomerular sclerosis (*C*), and fibrous organization of a thrombus in lupus nephrosis (*D*). (*A*, From Ehrich, Forman, and Seifter, A. M. A. Arch. Path., November, 1952.)

RENAL FAILURE

It has long been known that in Bright's disease renal failure is due frequently to shrinkage of the kidneys and that this is caused usually by glomerular obstruction,[1,25,37-39,59] Also, it was pointed out by Volhard and Fahr[59] and by Munk[51] that crescent formation was an important factor in glomerular obstruction and hence in renal failure. In fact, Volhard prided himself on his ability to diagnose extracapillary (crescentic) glomerular nephritis clinically on the basis of rapidly developing renal failure. Thrombosis of glomerular loops was not

considered as a cause of crescent formation and glomerular obstruction. It is noteworthy that glomerular thrombosis had been described repeatedly in diffuse hemorrhagic glomerular nephritis.[1,25,38,40,52] Also, it was seen in lipid nephrosis[10] and recently in intercapillary glomerular sclerosis.[4,30] Similarly, it had been known that intracapsular "fibrin clots" and crescents occur not only in focal embolic glomerular nephritis and diffuse hemorrhagic glomerular nephritis, but also in lupus nephrosis, intercapillary glomerular sclerosis, and even in lipid nephrosis.[10,19,25,59] If these changes were not connected with each other, this was due probably to the rapidity with which thrombi are collagenized and thus withdraw from recognition.[17,19]

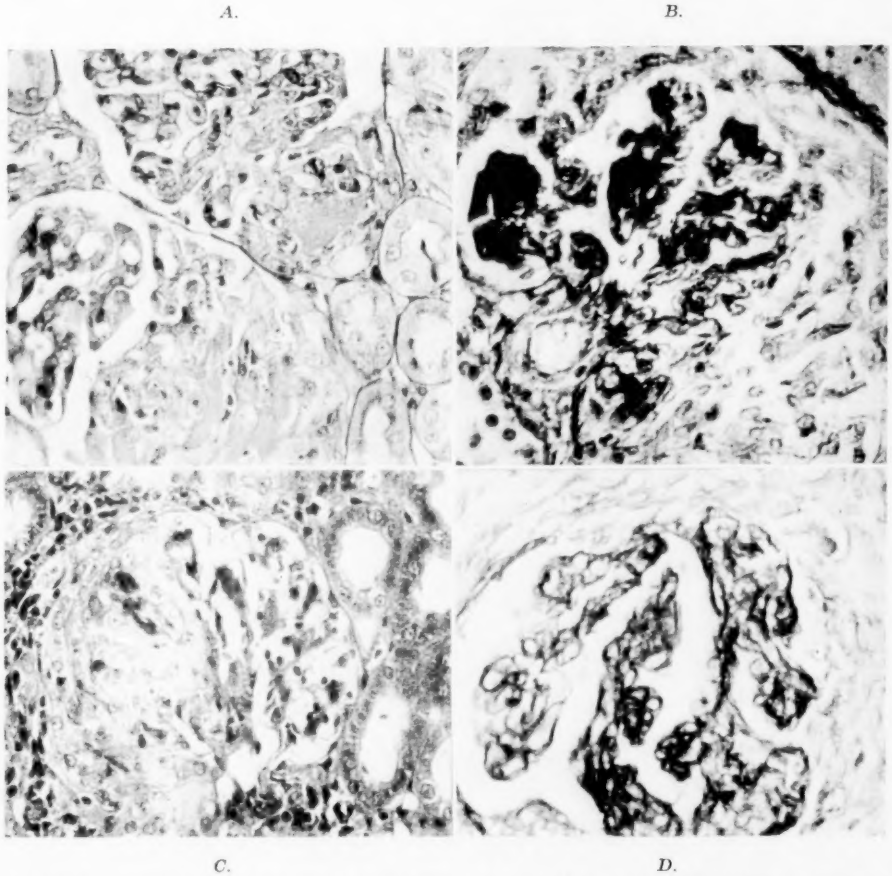

Fig. 3.—Exudation and subsequent organization of exudate by glomerular epithelium (crescent formation) following thrombosis and necrosis of capillary loops in nephrotoxic glomerular nephritis in a rabbit (*A*), in subacute glomerular nephritis in man (*B*), in foreign protein nephritis in a rabbit (*C*) and in lupus nephrosis in man (*D*). (*A-C*, From Ehrich, Forman, and Seifter, A. M. A. Arch. Path. November, 1952.)

Today, we know that renal failure may be due to tubular mechanisms, but usually it is glomerular in origin. Also, we know that glomerular failure may be caused, as mentioned above, by hyaline thickening of the filtering membrane (Fig. 1, *C* and *D*) and that in other instances it is the result of ischemia

due to inflammation (in acute hemorrhagic glomerular nephritis) or excessive deposition in the capillaries of abnormal protein (in amyloid nephrosis). A more common cause of glomerular failure, however, seems to be thrombosis of glomerular loops, followed by necrosis of loops and exudation into the capsular space, and by organization of the thrombotic material within the loops (focal sclerosis) and of the exudate in the capsular space (crescent formation). This mechanism is commonly observed not only in human and experimental glomerular nephritis and lipid nephrosis,[19] but also in human lupus nephrosis, intercapillary glomerulosclerosis, and malignant nephrosclerosis.[55] It is illustrated in Figs. 2 and 3.

It thus appears that the fate of a patient with glomerular disease depends in many cases on the presence or absence of thrombosis. While changes of the filtering membrane may subside without serious consequences, thrombi and crescents cannot be resolved but terminate in partial or complete obliteration of the glomerulus. If only a few glomeruli are affected by this complication, the patient may survive. However, if many are affected, the patient is doomed. Hence, crescents are prominent in patients who die early, that is, weeks or months after onset of a glomerular nephritis.

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IDENTITY OF GLOMERULAR NEPHRITIS

Nephritis is classified generally into ascending pyelonephritis, hematogenous pyogenic nephritis, specific nephritis, focal embolic glomerular nephritis, interstitial nephritis, and glomerular nephritis. While most nephritides are recognized entities, glomerular nephritis is still in doubt.[15] Is there one, or are there several glomerular nephritides? Is the glomerular nephritis caused by foreign protein identical with diffuse hemorrhagic glomerular nephritis, or is it a different entity? Are chronic nephritides with and without the nephrotic syndrome representatives of the same disease, or are they different maladies?

Clinical Observations.—The acute or initial stage of glomerular nephritis is characterized clinically, as is agreed, by hematuria, proteinuria, a rise in blood pressure, and other phenomena. While Volhard[58,59] stressed the hypertension, Addis[1] felt that the hematuria was the outstanding sign. Hence, Volhard spoke of diffuse glomerulonephritis, while Addis preferred the term hemorrhagic Bright's disease. At present, many writers use the term diffuse hemorrhagic glomerular nephritis.

Patients who survive the acute or initial stage of this nephritis, but do not recover, may immediately, or after various intervals of latency,[1] take a chronic hydropic or anhydropic course. The former differs from the latter by the presence of the nephrotic syndrome.

Chronic hydropic glomerular nephritis is known also as "mixed nephritis and nephrosis" apparently because early writers[51,59] believed that the nephrosis was tubular in origin. In the light of present knowledge, however, this view does not appear to be acceptable.

Recently, it was claimed by Ellis[24] that chronic hydropic glomerular nephritis is not related to diffuse hemorrhagic glomerular nephritis, but that it is a different nephritis (type II nephritis). It should be noted, however, that this

author did not distinguish between glomerular nephritis and lipid nephrosis. Also, he believed that the occurrence of renal failure in lipid nephrosis indicated that this had been a nephritis rather than a nephrosis.[19]

Volhard[58,59] found edema of more than 10 per cent body weight in half of his cases of acute hemorrhagic glomerular nephritis. He spoke of "nephritis with the nephrotic syndrome" if the edema did not recede but became an outstanding feature of the disease. Bloom and Seegal[12] noted a "nephrotic phase" in 50 per cent of their cases of chronic glomerular nephritis. The average duration of this phase was almost two years. According to Munk,[51] the nephrotic syndrome was frequently seen in trench nephritis, where it made its appearance sometimes in the fifth and sixth week after onset of the nephritis. On the other hand, Löhlein[39] stated that "the chronic parenchymatous nephritis of the clinicians" is almost always a sequel of acute glomerular nephritis. Similarly, Addis and Oliver[1] noted that the nephrotic syndrome as a phase in the progression of chronic glomerular nephritis is much more common than lipid nephrosis. Well-documented instances of this sequence of events have been reported repeatedly by competent observers.[1,6,51,56,59] These various observations leave little doubt that many cases of "chronic glomerular nephritis with the nephrotic syndrome" are primarily instances of hemorrhagic glomerular nephritis.

Morphologic Observations.—The renal lesion of patients who die during the *acute or initial stage of glomerular nephritis* is characterized by infiltration of the glomeruli with granulocytes, by escape of erythrocytes into the capsular space, and especially by endothelial proliferation[2,6,7,9,25,35,37-40,59] (Fig. 4,*A*). The filtering membrane is edematous, as was shown so well by Jones.[34] The edema causes separation of the various layers of the filtering membrane, but these remain connected by fibrils. The latter has been described by many observers.[8,9,19,44]

While most pathologists seem to believe that acute hemorrhagic glomerular nephritis should not be diagnosed in the absence of endothelial proliferation, Allen[2] distinguishes an "acute membranous glomerular nephritis" characterized by "soft fibrinoid swelling of the walls of the glomerular capillaries." His illustrations, however, all portray glomeruli of eclamptic kidneys. They show the eclamptic glomerulonephrosis, which was interpreted as degenerative by Fahr[25] and as noninflammatory by Bell.[9]

If death from acute hemorrhagic glomerular nephritis is due to renal failure, and this occurs during the first week of the disease, the glomeruli tend to be bloodless.[37-40,58,59] This is probably the reason why Volhard[58,59] believed that glomerular ischemia is an important factor in the pathogenesis of glomerular nephritis. Also, it is the reason apparently why Fahr[25,59] felt that intracapillary thrombosis is not a significant feature of this disease. However, the histologic appearance of the glomeruli may be quite different in patients who survive the disease, or if death is not due to renal failure, or if renal failure occurs later during the disease. That this may well be so is apparent from experimental observations in rabbits[23] and from autopsy studies of cases of subacute glomerular nephritis. The latter are characterized by the development of numerous crescents due to thrombosis of glomerular capillaries.

Endothelial proliferation of the glomeruli also is commonly found in various infectious diseases.[6,22,32,46] Not only has this been shown to be a common feature of these diseases, but it was also observed that the degree of proteinuria which occurs in these diseases tends to parallel the endothelial proliferation. The morbid significance of this reaction is not certain. It may well be indicative of a mild diffuse hemorrhagic glomerular nephritis.

The glomerular lesion of patients who die from *chronic glomerular nephritis* may be characterized predominantly by endothelial proliferation followed by hyalinization of the filtering membrane (Fig. 1, *D*) (intracapillary glomerular nephritis), or by fibrosis of the tuft associated with epithelial proliferation (crescent formation) (Fig. 3, *B*) followed by hyalinization of both the tuft and crescent (extracapillary glomerular nephritis). In most cases, however, we find various combinations of the two.

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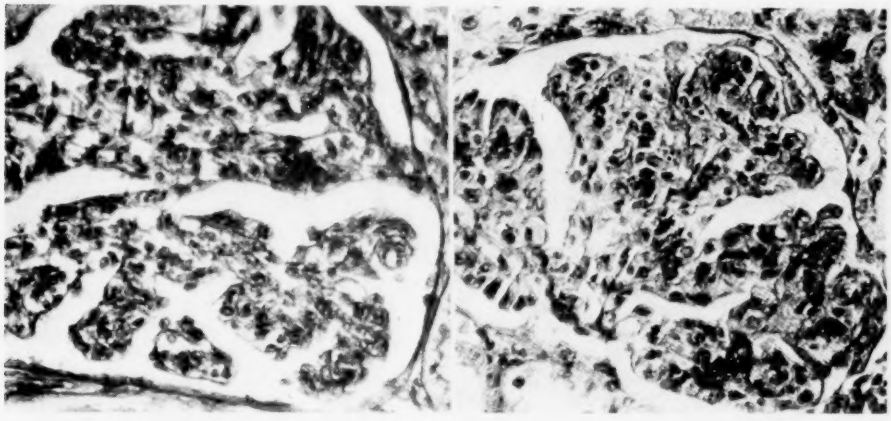

A. *B.*

Fig. 4.—Acute diffuse hemorrhagic glomerular nephritis in a 7-year-old child (*A*) and in a rabbit treated with nephrotoxic serum (*B*). (From Ehrich, Forman, and Seifter, A. M. A. Arch. Path., November, 1952.)

Löhlein[38] knew that extracapillary glomerular nephritis is seen especially in patients who develop renal failure early during the disease ("stormy type"), while intracapillary nephritis prevails in patients who die after many years ("mild type"). Similarly, Volhard[59] believed that it was the extracapillary glomerular nephritis which did not heal and that the duration of the disease depended on the degree of extracapillary involvement. Similar views were expressed by Fahr[25,59] and Munk.[51] These observations are well explained by our demonstration[17,19] that crescent formation is due to thrombosis of glomerular capillaries.

In regard to the hydropic and anhydropic courses of chronic glomerular nephritis, Löhlein[39] noted that kidneys with many crescents showed little fatty infiltration of the tubular epithelium, while kidneys without crescents revealed severe fatty degeneration. Similarly, Munk[51] observed the nephrotic syndrome chiefly in patients whose kidneys showed only little or no crescent formation.

Observations such as these suggest that it is the intracapillary rather than the extracapillary glomerulitis which causes the nephrotic syndrome in glomerular nephritis.

Experimental Observations.—Diffuse hemorrhagic glomerular nephritis can be reproduced in rabbits (Fig. 4,*B*) and in rats[21] by means of antikidney serum, as was shown first by Masugi.[43] Some investigators[29,43] continue to claim that it can be elicited also by intravenous injection of foreign protein (horse serum,

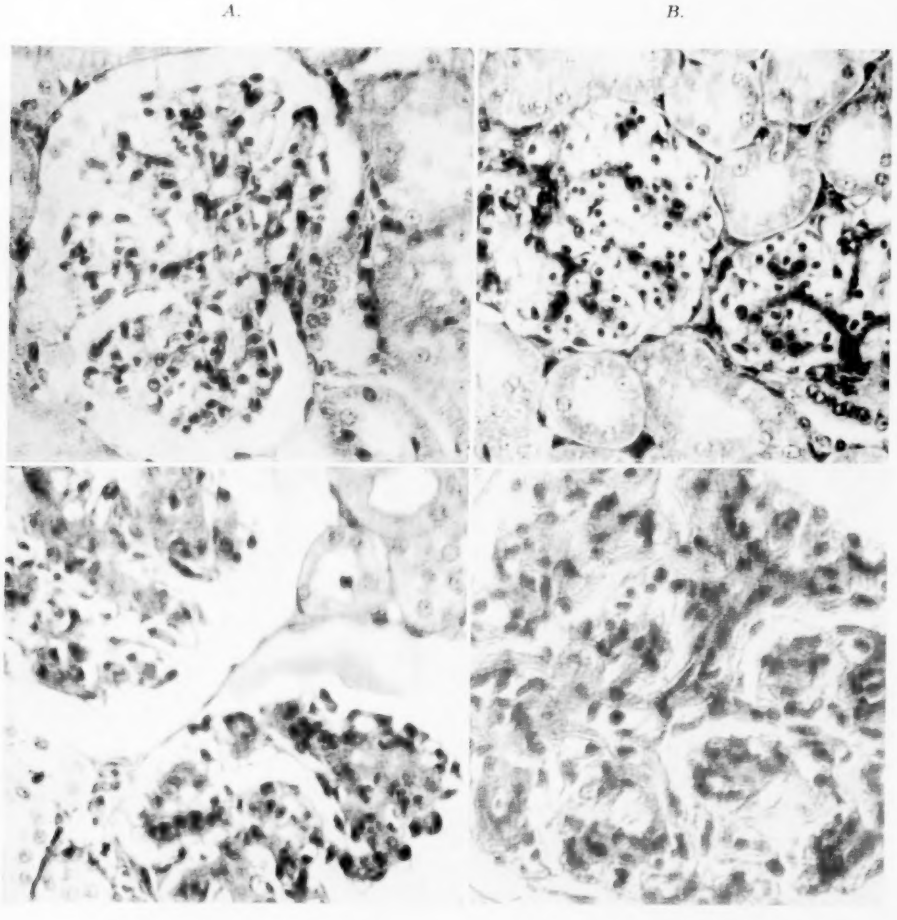

Fig. 5.—Intercapillary glomerular nephritis produced in rabbits by horse serum (*A-C*) as compared to intercapillary glomerular sclerosis in human diabetes (*D*). Rabbit B received horse serum alone, C horse serum and DCA, while A served as a normal control. (*A-C* From Ehrich, Forman, and Seifter, A. M. A. Arch. Path., November, 1952.)

gamma globulin). The latter view is appearently based not on the basic lesion of the experimental disease, but on its frequent complication by intracapillary thrombosis and its consequences.[19] This, however, is an unspecific reaction, as was pointed out repeatedly in the present paper.

The basic lesion in foreign protein nephritis differs from that of diffuse hemorrhagic glomerular nephritis in that it appears to be a reaction essentially of the intercapillary space[19] (Fig. 5, *A* to *C*). In fact, we have used this lesion as an argument that the glomerulus contains an intercapillary space (mesangium). According to McManus[45] "there is now good agreement that there is an intercapillary space." The difficulties which were encountered by Hall[28] and others "have been resolved by the recent description of the anatomy of the glomerulus by Mueller, Mason, and Stout."[49]

The two diseases also differ clinically. Further, the foreign protein nephritis appears to be not so much a renal disease as part of serum sickness, that is, a collagen disease with prominent involvement of heart and arteries. This view is now shared by many workers.[33,60]

The nature of the intercapillary disease requires further study. The occurrence of a similar alteration in diabetes mellitus (Fig. 5,*D*) and the observation that in this disease it may be followed by the deposition of collagen fibers suggests that this is not an endothelial reaction.

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IDENTITY OF LIPID NEPHROSIS

The nephroses may be divided into tubular and glomerular nephroses, as I recommended many years ago.[16] The tubular nephroses fall into two groups, those which are due largely to storage in the tubular epithelium of filtered materials such as glucose (glycogen), lipids, proteins, bile, malanin, iron, or therapeutic agents such as gelatine (storage nephroses), and those which are caused by necrosis of tubular epithelium (toxic and anoxic nephroses). While storage nephroses may be clinically silent, toxic and anoxic nephroses tend to cause renal failure and death.

The best known glomerular nephroses are amyloid nephrosis, intercapillary glomerular sclerosis, lupus nephrosis, and lipid nephrosis. They differ from the tubular nephroses clinically in that they may give rise to the nephrotic syndrome as well as to renal failure.

While most nephroses are well-defined entities, the identity of lipid nephrosis is contested. Thus Löhlein[41] claimed that with the exception of amyloid nephrosis, "chronic parenchymatous nephritis" is invariably a late state of diffuse hemorrhagic glomerular nephritis because of the presence of nephritic changes in the glomeruli "in almost all cases of this clinical entity." He admitted, however, that it could not be proved that the morphologic changes which Fahr[59] and he[41] saw in "pure" cases of lipid nephrosis were residues of a glomerulonephritis. Hence, he considered the possibility that this may have been a different reaction, "that the diffuse injury in this disease did not cause an outspokenly inflammatory reaction; in other words, that in these kidneys acute glomerular nephritis never develops."

Similarly, Bell[7] stated that lipid nephrosis "represents a variety of acute nephritis." Later,[8] he spoke of "membranous glomerulonephritis," but he said "it is not known whether or not membranous glomerulonephritis has a different etiology from the proliferative form." In 1946,[9] he concluded that "from the histologic point of view lipid nephrosis is different from proliferative glomerulonephritis, but it is possible that the histologic pictures represent different

types of reaction to the irritant. The same injurious agent might in some patients produce no reaction, in others a thickening of the basement membranes, and in others endothelial proliferation." Also, he agreed with Schlayer,[54] Munk,[51] and others that "there are cases which show transitions histologically between membranous and proliferative lesions."

Löhlein and Bell believed that lipid nephrosis was a variety of diffuse hemorrhagic glomerular nephritis but that they were different pathogenetically. Ellis[24] felt that anhydropic and hydropic glomerular nephritis were different diseases (type I and type II nephritis) and that lipid nephrosis was the same as chronic hydropic glomerular nephritis (type II nephritis). The latter view was based on the observation that patients with chronic lipid nephrosis may ultimately be indistinguishable from patients with the nephritic disease.

Similarly, Allen[2] asserted that chronic lipid nephrosis was the same as "chronic membranous and lobular nephritis," and the "pure" and "mixed" nephroses were merely "different grades of development of the same disease." He stated that the "pure" form may progress to the "mixed" type or even to a form of chronic azotemic glomerular nephritis.

It has been pointed out elsewhere[19] that clinical observations of this kind are in keeping with the older findings of Blackman[10,11] as well as with the results of recent studies by various pediatricians.[5,13,27,42,47] The interpretation by Ellis and Allen of these observations, though in accord with those of previous clinicians and pathologists,[8,32,37-41,51,54,58] however, is not acceptable. The development in lipid nephrosis of hyposthenuria, hypertension, and azotemia, clinically, or of glomerular scars, adhesions, and crescents, anatomically, does not indicate that the patient has glomerular nephritis, but it signifies merely that lipid nephrosis, like other glomerular nephroses, may terminate in renal failure and that this, if it occurs, is caused by glomerular obstruction.[17,19,42] According to recent observations, renal failure occurs in some 50 per cent of all children who have lipid nephrosis.[13]

Recently, Allen[3] has likened his "membranous glomerulonephritis" to his "verrucal endocardiosis," calling the one an "itis" and the other an "osis." Also, he has observed that "chronic lobular glomerulonephritis" is almost always associated with hypertension and often with renal insufficiency and, therefore, should be looked upon as "a more fulminant variant of membranous glomerulonephritis in which the walls of many of the glomerular capillaries have undergone marked fibrinoid swelling and even coalescence, and in which exudative and proliferative glomerulonephritis have often been superimposed." Allen did not consider the possibility that his "lobular glomerulonephritis" might be merely the result of complication of his membranous glomerulonephritis by thrombosis and subsequent fibrosis of glomerular loops previously affected with the lesion of lipid nephrosis. That this is the more likely explanation is apparent from observations on renal failure and also from experiments in rats in which this lesion can be reproduced (Fig. 6,*D*).

Recently, we[21] have presented new evidence to show that in rats small doses of antikidney serum produce diffuse proliferative glomerulonephritis (Figs. 6,*A* and *C*), while large doses of the same serum cause the picture of lipid

nephrosis (Fig. 6,*B*). This should be evidence enough that we believe the etiology of diffuse hemorrhagic glomerular nephritis and that of lipid nephrosis to be closely related, if not the same.

However, pathogenetically, glomerular nephritis and lipid nephrosis are not the same. It is true that no objection can be raised to the statements of Bell[8,9] and Allen[2,3] that the lesion in lipid nephrosis is primarily a nephritis, for the situation resembles that of "fibrinoid degeneration," which, too, may be

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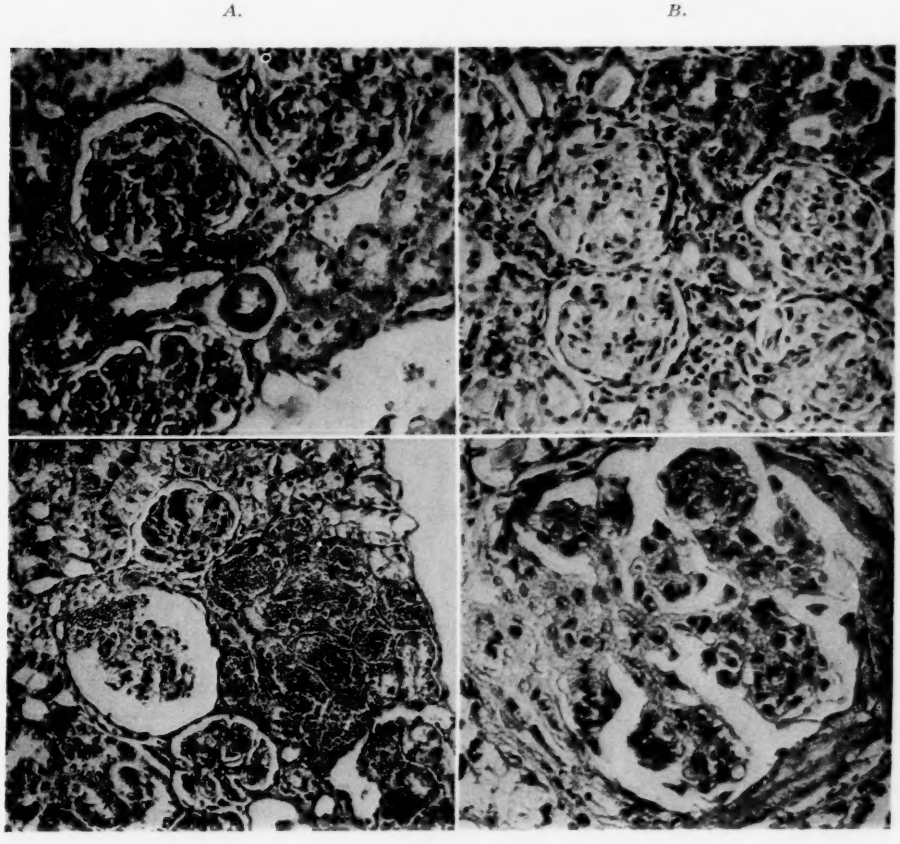

Fig. 6.—Proliferative glomerular nephritis (*A*) and regressive lipid nephrosis (*B*) produced in rats by 0.075 (*A*) and 0.2 (*B*) ml. of the same antikidney globulin. Also shown are hematuria in a rat treated with a small dose of antikidney serum (*C*) and "lobular glomerulonephritis" (lipid nephrosis with organized thrombi in glomerular loops) in a rat treated with a large dose of antikidney serum (*D*).

looked upon as an inflammatory lesion.[18] However, whether or not one speaks of inflammation, it must not be overlooked that *in diffuse chronic hemorrhagic glomerular nephritis the lesion is progressive (productive), while in lipid nephrosis it is regressive (degenerative). The progressive lesion causes a clinical picture entirely different from that of the regressive lesion. Also, the prognosis of the two is not the same.*

However, there is an even more cogent reason why we should regard glomerular nephritis and lipid nephrosis as different diseases. It was pointed out earlier in this review that modern classification of disease is based on the pathogenetic principle. Now it was shown that the two diseases may be etiologically the same but that they differ in their pathogenesis. However, if the identity of a disease is determined by its pathogenesis and this is different in diffuse hemorrhagic glomerular nephritis and lipid nephrosis, then logic permits only one conclusion, namely, that *the two diseases are not the same.*

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MICROBIOLOGIC ASPECTS OF GLOMERULONEPHRITIS

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SPECIFIC information concerning the microbiologic aspects of glomerulonephritis is meager primarily because modern bacteriologic and serologic techniques have not been employed widely in the study of kidney disease. Much of our knowledge relating to the cause of nephritis has been derived from sequential associations with various diseases including scarlet fever, respiratory infection, and pneumonia. Few investigations have included bacteriologic and serologic examinations of a large group of patients with acute renal disease. Today, the problem becomes complicated because most acute infections are treated by the physician in the home prior to the development of signs or symptoms of nephritis. Modern antibacterial therapy alters the flora of the respiratory tract, making isolation of the bacterium responsible for kidney disease difficult, if not impossible. For this reason present day studies of the bacteriologic flora of patients with nephritis are difficult to interpret.

The recognition of the role of the Group A streptococcus in glomerulonephritis is intimately related to the development of our knowledge of scarlet fever. In the original description of Bright,[1] nephritis was described as a complication of scarlatina or other acute infections. Although some seventy-five years later it was recognized that long chains of streptococci could be demonstrated in the exudates obtained from patients with scarlet fever, similar organisms could be isolated from other infections. Thus, a causal relationship of the streptococcus to scarlet fever was difficult to establish. Dick and Dick,[2] in 1923, produced in man both scarlet fever and tonsillitis not associated with a cutaneous rash by the inoculation of streptococci obtained from a patient with scarlet fever. These studies established the streptococcal etiology of scarlet fever and also emphasized the fact that simple respiratory infections characterized by a sore throat were produced by the same organism. In the meantime, acute glomerulonephritis was observed to develop as a late complication following attacks of scarlet fever.[3]

It was natural to accept the streptococcus as an important cause of acute nephritis, since many patients gave a history of scarlet fever which preceded the onset of the kidney disease. In recent years, scarlet fever has not played

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a dominant role as a cause of nephritis. For example, Osman,[4] in 1933, observed that scarlet fever was the initiating infection in only 8 of 235 cases of acute nephritis. Hayman and Martin,[5] in 1940, reviewed 976 cases of nephritis and only 6 per cent developed the disease following scarlet fever. The majority of patients, 66 per cent, developed signs of nephritis following an acute respiratory illness. According to the history, the patients frequently complained of a sore throat, a characteristic feature of a streptococcal infection. In the series of 62 patients studied by Hayman and Martin,[5] beta hemolytic streptococci were isolated from 55 per cent of the cultures obtained from the nose or throat. Other investigators have found these organisms in 80 to 100 per cent of patients at the time of the onset of nephritis.[6,7] The cause for the rather marked variation in the number of patients with acute nephritis showing positive cultures for beta hemolytic streptococci is not known. Some of the failures are undoubtedly due to inadequate techniques for isolation of small numbers of streptococci. The bacteriologic results obtained in patients with nephritis are similar to those obtained in patients with rheumatic fever or in patients who have recovered from a streptococcal infection.[8] That streptococci are responsible for most cases of nephritis can only be determined by the study of streptococcal antibodies in addition to the employment of bacteriologic techniques.[6,9]

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Addis,[10] in his monograph, states that all positive evidence indicates that a beta hemolytic streptococcal infection invariably precedes the onset of acute nephritis. In most reported instances where the kidney complication developed after pneumonia and other infections, there is insufficient evidence to eliminate the streptococcus as the etiologic agent. In addition, some observers have noted that the clinical course of nephritis developing after nonstreptococcal infections is different from that exhibited by patients who develop nephritis following infection with the streptococcus.[11] Therefore, the present discussion will be limited to the streptococcus as a cause of initial attacks of acute glomerulonephritis.

In view of the fact that beta hemolytic streptococci may be isolated from many normal individuals, the interpretation of positive cultures obtained from patients with nephritis is difficult. Cultures from normal carriers usually show few colonies on the blood agar plates and many of the stains belong to Lancefield Groups B, C, F, or G. These serologic groups rarely cause respiratory disease.[12] Pharyngeal cultures from individuals with scarlet fever or streptococcal respiratory infections almost invariably show Group A streptococci. The organisms are usually isolated in large numbers and produce M protein. Because they produce M protein, they can be identified as belonging to one of more than 40 types of Group A organisms. Following infection with Group A streptococci, the number of organisms present in the throat gradually decreases and after several weeks the streptococcus loses its ability to produce M protein and is no longer typable.

As mentioned previously, oropharyngeal cultures from patients with nephritis frequently fail to exhibit Group A streptococci on blood agar plates. In many instances this is due to prior therapy with one of the antibacterial drugs. Some information concerning the organism responsible for the kidney

disease may be obtained in this situation by culturing the immediate members of the family. Experience has demonstrated that the streptococcus responsible for the case of nephritis can frequently be isolated from the contacts in the household.[13]

Streptococcal disease is unique among bacterial infections because of the nonsuppurative complications, acute rheumatic fever, and acute glomerulonephritis. Since rheumatic fever is observed following infection with any of the serologic types of Group A streptococci and the attack rate is relatively constant, the number of cases of acute rheumatic fever should be an index of the number of cases of streptococcal infection in the population. Seegal, Seegal, and Jost,[14] in a tabulation of admissions for nephritis and rheumatic fever in various hospitals throughout the country, found that the number of cases of nephritis bore little relation to the number of cases of rheumatic fever. These data would indicate that the prevalence of acute nephritis does not necessarily reflect the number of streptococcal infections in the community. This observation was confirmed by a review of clinical studies of scarlet fever which showed that the attack rate of nephritis varied considerably.[15]

In an attempt to explain these epidemiologic differences between acute rheumatic fever and acute nephritis, the existence of nephritogenic strains of streptococci was postulated. A review of the early literature concerned with the serologic identification of Group A organisms isolated from patients with scarlet fever and other respiratory disease failed to incriminate any single streptococcal type as being responsible for the kidney complication. In most of these early studies the agglutination method for typing streptococci was employed. This technique is difficult to perform and cross reactions are common, so that interpretation of the available data is difficult. Nevertheless, it is interesting that Ehinger[16] obtained some evidence of a variation in the nephritogenic ability of the streptococcus. In a group of 26 patients with infections due to type 31 streptococci, 6 subsequently developed nephritis. Kidney complications were observed rarely after infection with other types.

Beginning in 1949, streptococci isolated from cultures of the oropharynx obtained from patients with acute glomerulonephritis and from their family contacts were classified serologically. These studies[15] showed that streptococci of types 12 and 4 were especially likely to be associated with nephritis.* These investigations have been continued and are summarized in Table I. Of 83 cases of nephritis where a streptococcus was isolated from either the patient or from the parents or siblings in the home, type 12 streptococcus appeared to be responsible for the disease in 78 per cent. Type 4 accounted for 18 per cent of the cases. From 4 patients, two different serologic types were identified in the cultures. Since multiple colonies were not routinely selected from the blood agar plate, it is possible that other patients may have harbored more than one type of Group A streptococcus. In 2 patients, an organism was isolated which could not be identified with the available typing sera.

*Two cases of nephritis were thought to be related to type 18 streptococcus, but subsequent investigation showed that these organisms were type 4.

TABLE I. SEROLOGIC TYPES OF STREPTOCOCCI ISOLATED FROM SPORADIC CASES OF ACUTE NEPHRITIS (1949-1956)

NUMBER OF PATIENTS	SEROLOGIC TYPES
62	12
15	4
1	25
2	12 and 19
1	1 and 6
1	19 and NT*
1	NT*

*Not typable with the available antisera.

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Other investigations of the serologic types of streptococci isolated from patients with nephritis were summarized in 1953.[15] In a total of five epidemics in which 63 cases of nephritis were observed, type 12 streptococci were responsible for the kidney disease. In a study of sporadic cases of nephritis from 1936 to 1942, Wertheim and his co-workers[17] isolated typable Group A streptococci from 39 patients with acute glomerulonephritis, and 51 per cent had organisms identified as type 12.

More recent studies have emphasized the nephritogenic qualities of the type 12 streptococcus and, in addition, evidence has been obtained which indicates that other serologic types may possess the ability to produce kidney disease. Reed[18] described an epidemic of type 12 infections in Nova Scotia, where 22 patients developed nephritis. Siegel, Rammelkamp, and Griffeath[13] studied a small outbreak of type 12 infections in a nursery school in Wyoming and seven examples of nephritis were recognized. In England, Wilmers, Cunliffe, and Williams[19] isolated type 12 streptococci from 28 of 31 sporadic cases of acute nephritis. In a large epidemic of nephritis in a military installation in Maryland, Stetson and his colleagues[20] were able to show that kidney complications were regularly associated with type 12 infections. In this outbreak, a total of 147 patients exhibited the classical features of acute nephritis.

Additional studies have been conducted in Hawaii, where an increased incidence of nephritis has been observed for several years.[21] Cultures of the pharynx from patients with acute nephritis as well as studies of type specific antibodies in children who had recovered from an attach showed that the outbreak was due to type 4 streptococci. The study of type-specific antibodies has proved to be a valuable tool in the investigation of the role of the streptococcus in nephritis. Preliminary results obtained in Cleveland, Ohio, show that children who have recovered from acute nephritis usually exhibit antibodies to a nephritogenic type of streptococcus.[9]

Type 25 infections of the respiratory tract are relatively rare; however, in addition to the case studied by Feldman and reported elsewhere,[15] Bennike and his colleagues[22] observed a patient in Copenhagen with a type 25 infection who subsequently developed signs and symptoms of nephritis.

Of considerable interest is the epidemic of scarlet fever and nephritis reported by Kleinman.[23] In this outbreak at an Indian Reservation at Red Lake, Minnesota, 63 cases of nephritis were recognized. Cultures from the respiratory

tract and from skin lesions revealed a strain of streptococcus which could not be identified with the available typing sera. Updyke, Moore, and Conroy[24] have identified this strain and have suggested that it be called Red Lake until assigned a number.

At the present time there is little doubt that only a few strains of Group A streptococci possess the ability to induce acute nephritis. The majority of the strains belong to serologic types 12, 4, and Red Lake. In addition, infection with type 25 may possibly cause nephritis. Although other serologic types have been isolated from patients with acute nephritis, further experience is required to ascertain their relationship to the kidney disease. It is important to obtain added information concerning the strains and serologic types of streptococci associated with nephritis in various parts of the world because through such studies it may be possible to define the characteristics of the organisms which produce kidney disease.

Little is known concerning the biologic characteristics of nephritogenic streptococci in comparison to other serologic types. On blood agar plates colonies of type 12 streptococci are small and white. Large mucoid colonies have not been observed. Experience with streptococci belonging to types 4 and 25 has been limited, but these colonies likewise appear white. Perhaps the most unusual characteristic observed thus far is the reaction of nephritogenic types of streptococci to infection with bacteriophage. Preliminary studies, presented in Table II, show that there is lysis of many strains of streptococci belonging to types 12, 4, and 25 following infection with bacteriophage, whereas streptococci belonging to other serologic types seldom exhibit this reaction. These results would indicate some common biologic feature among nephritogenic organisms. In view of the fact that bacteriophage may convert strains of avirulent diphtheria bacilli into toxigenic organisms,[25] it seems possible that bacteriophage may play a role in acute nephritis. Further studies will be required to define this relationship.

TABLE II. SUSCEPTIBILITY OF DIFFERENT SEROLOGIC TYPES OF GROUP A STREPTOCOCCI TO INFECTION WITH BACTERIOPHAGE

TYPE OF STREPTOCOCCUS	NUMBER OF STRAINS	PER CENT SHOWING LYSIS
3	26	4
4	18	39
5	2	0
12	226	71
14	19	0
18	7	0
19	27	0
25	1	100
30	23	0
Red Lake	1	100

SUMMARY

Through the study of the bacteriologic flora of the respiratory tract in patients with nephritis, it is becoming increasingly clear that the Group A strepto-

coccus is responsible for the majority of acute attacks. The evidence is now sufficient to establish the fact that only a few strains of Group A organisms are capable of producing nephritis. Nephritogenic streptococci may usually be classified as type 12, 4, or Red Lake. Type 25 streptococci may also possess nephritogenic qualities. Further studies of these organisms may assist in the elucidation of the pathogenesis of acute glomerulonephritis.

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IMMUNE REACTIONS IN HUMAN GLOMERULONEPHRITIS

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THE association of glomerulonephritis and infection of the upper respiratory tract was noted in the early description of nephritis.[1] The nature of the infection usually preceding acute nephritis has been defined by studies incriminating Group A hemolytic streptococci, predominantly of certain types.[2] The manner in which these infections result in acute nephritis remains obscure. The action of direct nephrotoxins has been postulated and warrants further study in view of the association of certain types of streptococci with acute nephritis. An attractive hypothesis, not incompatible with the possibility of an associated nephrotoxic agent, arose shortly after the characterization of serum sickness as an allergic reaction by von Pirquet and Schick in 1905. The nephritis which occasionally developed following scarlet fever was known to occur after a latent period of two to four weeks. Escherich and Schick[3] noted that this latent period was similar to that required for the development of serum sickness and suggested allergy to the preceding infection as a cause of glomerulonephritis.

In an analysis of experience at the London Fever Hospital from 1879 to 1888, Goodall[4] confirmed earlier observations concerning the occurrence of a latent period and tabulated the maximal frequency for the onset of nephritis at the twentieth to twenty-fourth day after the beginning of scarlatina.

Of particular interest in this respect is the study by Lyttle.[5] A sudden explosive increase in urinary red cells, white cells, and casts, by Addis counts, occurred in 14 patients about two weeks after the onset of scarlet fever. None of these patients developed clinical acute nephritis. The occurrence of these abnormalities after an interval of two weeks, during which baseline studies were established, suggests a reaction to the infection which occurs at the time of the appearance of antibodies to the infecting organism. The urinary abnormalities are qualitatively, but not quantitatively, similar to those of clinically apparent acute glomerulonephritis. In a group of patients who were being followed carefully for the development of hematuria following streptococcal infection, Stetson and associates[6] described a latent period of six to sixteen days with a mean of ten days. Obvious clinical manifestations of acute nephritis, when present, occurred after the onset of hematuria.

A review of the literature concerning the latent period of acute nephritis is presented by Seegal and Earle.[7] In addition, data are presented to illustrate

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the shortened latent period for the development of exacerbations of chronic nephritis, a phenomenon which may have a parallel in the accelerated response of recurrent serum sickness.

Other clinical manifestations in human glomerulonephritis have been advanced as evidence of an allergic pathogenesis, but are less acceptable. The occasional association of manifestations of nephritis with nonthrombocytopenic purpura, serum sickness, or other allergic reactions such as sensitivity to poison oak[8] or poison ivy[9] have been cited by some observers. Attempts have been made to define an allergic diathesis in acute nephritis by correlating the occurrence of nephritis with the presence of distinctly different allergic reactions such as asthma or eczema, or with hypersensitivity reactions to various antigens.[10] Antibody responses and allergic reactivity to different antigens in different sites are frequently independent in the same individual. Normal individuals simultaneously immunized with different types of pneumococcus polysaccharides may react with comparatively good antibody production to one antigen and poorly to another.[11,12] It would be impossible to characterize such normal individuals as hyperreactors or hyporeactors except in terms of the specific antigen involved.

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The fallacy of attempting to implicate nephritis with the coexistence of other immune phenomena is apparent in a consideration of rheumatic fever. Rheumatic fever and acute nephritis have both been related to streptococcal infections and, with some reservations, have been thought to result from allergic mechanisms,[13,14] although biologic differences have been emphasized between the two diseases.[7] The striking differences in attack rates of rheumatic fever and acute nephritis following streptococcal infections of various types,[15] and the failure of these diseases to coexist more frequently than could be accounted for on the basis of chance alone suggested to Stetson and associates[6] that the pathogenetic mechanisms for the development of these complications of streptococcal infection are not "similar or even related." The immune or allergic response is characterized by its serologic specificity[16,17] and also to some degree by the uniqueness of the allergic reaction in vivo.[18,19] The mechanism for both diseases may be allergic without necessarily involving a contingent incidence, a related antigen or a related shock organ. The unique and independent response of the same individual to different pneumococcus polysaccharides[11,12] exemplifies this specificity of antibody response even when the antigens are grossly similar chemically. With the high degree of specific reactivity characteristic of immune reactions, it is entirely possible that both diseases may result from allergic mechanisms to totally dissimilar antigens in streptococci. The antigen related to nephritis might occur in but a few types and the other may be generally distributed throughout all Group A organisms. Reactions to these antigens would then be entirely independent of one another and the resulting diseases would not be expected to coexist more frequently than could be accounted for by chance alone.

The evolution of the studies on experimental nephritis has contributed substantially to the development of the allergic hypothesis for the pathogenesis of acute and chronic nephritis.[20] In the human disease, data derived from

serologic evidence have lent further support to that view, perhaps more convincing than the clinical features discussed above.

The serologic data may be considered in two categories: first, those serologic changes related to the preceding streptococcal infection; and, second, those serologic reactions thought to be related particularly to the occurrence of an allergic type of reaction.

SEROLOGIC CHANGES REFERABLE TO THE PRECEDING STREPTOCOCCUS INFECTION

Numerous serologic changes occur in acute glomerulonephritis which are a result of the preceding streptococcal infection. These include the development of antibodies to most of the known antigenic fractions of Group A streptococci including streptococcal nucleoproteins,[21,22] streptolysin-O,[23-25] C polysaccharide,[21] and streptokinase.[26]

The simultaneous study of antistreptolysin, antihyaluronidase, and antistreptokinase in various types of streptococcal infections did not reveal any significant differences in the immune response to the corresponding antigens following infection with "nephritogenic" strains.[6] Stetson and his co-workers[6] found that patients with types 3 and 6 streptococcal infections developed higher antistreptolysin titers than did patients with type 12 infections, although the incidence of nephritis was much higher following infection with the latter type. Within the group with type 12 infection, however, there was a suggestion of a higher antistreptolysin response in the patients who developed marked hematuria than in those with mild or no hematuria.[6] Lyttle and associates[25] observed that the height and duration of the abnormal antistreptolysin titer in patients with acute glomerulonephritis appeared to be related to the severity and persistence of the streptococcal infection but was independent of the severity of acute nephritis or the tendency to develop chronic nephritis.

Although little difference in antibody response to most streptococcal antigens can be discerned in acute nephritis, the frequency of occurrence of antibody to certain type-specific M proteins may be expected to follow the pattern of the type of preceding infection. It is clear from the studies of Rammelkamp and his co-workers[2,6,15] that relatively few types of streptococci may be responsible for most cases of acute nephritis. In this regard, the occurrence of epidemics of acute nephritis, including familial outbreaks, and the variable attack rates of nephritis following scarlet fever are cited,[15] as well as epidemiologic studies in the Armed Forces,[6] and in civilian populations at various American cities from 1949 to 52.[15] A review of experience during an earlier time interval, 1936 to 1942, at one institution in New York City was presented by Wertheim and his co-workers.[27] They found that streptococci cultured from patients with nephritis were also predominantly type 12. The organism associated with most cases of acute glomerulonephritis over many years and in different locales seems, therefore, well established. Less frequently, a few other types may be implicated.[2,6,15,27]

From these observations, an explanation may be derived for the relative rarity of repeated attacks of acute nephritis, even following known streptococcal infections.[7,28-30] This circumstance could not be explained by an allergic hypo-

thesis for the pathogenesis of acute nephritis and, indeed, argued against that hypothesis.[31] If the disease develops after infection with one of only a few types of Group A streptococci, and type-specific immunity also develops following that infection,[32] there is little probability of subsequent infection with another nephritogenic type of streptococcus.

In chronic nephritis and in nephrosis, the insidious onset and chronicity make the accumulation of data concerning an initial infection more difficult. The antistreptolysin titer in chronic nephritis is generally low, and in the nephrotic individual it may be extremely low.[26,33] Following streptococcal infections, however, antibody response to streptolysin O is readily observed in chronic nephritis and in children with nephrosis. It usually bears little noticeable relationship to the progression of the disease.[33] More noteworthy is the relationship of the antistreptolysin titer to the exacerbation which occasionally occurs in chronic nephritis. Earle and his co-workers[34] described 33 exacerbations in 15 of 81 patients with chronic glomerulonephritis. All 15 patients had one or more exacerbations of nephritis following streptococcal infections. Of the 33 exacerbations, 24 were preceded by streptococcal infection, as evidenced by a rise in antistreptolysin titer. In 6 instances, exacerbation was not associated with a rise in titer, although 2 of these were associated with preceding hemolytic streptococcal infection. In an earlier study of 68 patients comprising part of this group of 81, it was found that 322 other infections had occurred, including 48 known streptococcal infections, without the occurrence of exacerbations.[35] The immune response to the streptococcal infection therefore provides striking evidence of the relationship of that infection to exacerbations in chronic nephritis. The latent period for the development of the exacerbation in this study was one to four days, in contrast to the longer latent period for the development of acute glomerulonephritis.[7] Also, unlike acute nephritis, a correlation was noted between the magnitude of rise in antistreptolysin titer and the incidence of exacerbation of chronic nephritis.[34]

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SEROLOGIC CHANGES APPARENTLY RELATED TO THE NEPHROTIC PROCESS

The second category of immune responses which have been studied in glomerulonephritis are those thought to indicate the occurrence of an allergic process unique for nephritis and distinct from the immune response to streptococci.

Projecting the concept of isoantibodies as employed in experimental nephritis, attempts have been made to determine the presence of circulating autoantibodies to kidney tissues in patients with nephritis. Positive agglutination reactions were described when sera from patients with acute and chronic nephritis were mixed with collodion particles coated with an extract of renal tissue.[36] Lange and his associates[57] examined the sera from 23 patients with nephritis in various stages, including 4 with acute glomerulonephritis. The serum from 18 of the 23 patients (78 per cent) caused agglutination of collodion particles coated with renal tissue extracts. All 11 patients with chronic nephritis of over one year's duration demonstrated agglutinins, but the titer apparently varied from determination to determination. As controls, 33 normal young adults were

studied, as well as 35 patients with various diseases. The control sera exhibited weakly positive reactions on some occasions. A similar type of reaction, the agglutination of collodion particles coated with a heart extract, was observed by Cavelti[37] in rheumatic fever. Adequate controls are frequently not employed in this type of experiment. Sera should be used from disease states of an inflammatory nature bearing some relationship to the system studied. Extracts of organs other than the kidney are also desirable as antigen controls; and in all instances bacterial contamination of the organs should be kept in mind as a possible antigenic component. The collodion particle test is an extremely variable one. Even with a valid positive reaction, the question remains whether the reaction observed is merely a false positive Wassermann reaction, since the antigen employed may approximate the Wassermann antigen.[38] Indeed, in a similar study, syphilitic sera more regularly agglutinated particles coated with heart or kidney tissue extracts than did rheumatic sera.[39] This criticism also emphasizes a well-established observation, that autoantibodies may exist in the blood stream without apparent damage to tissues. This occurs in syphilis[38] and has been described in rabbits by Kidd and Friedewald.[40]

In the early postscarlatinal state, Schwentker and Comploier[41] found that human serum mixed with rabbit kidney extract caused complement fixation. Similar reactions were obtained in a small percentage of normal individuals. It is significant that of the 40 postscarlatinal patients who had complement fixing antibodies, only 2 developed mild nephritis. This emphasizes the lack of relationship of these antibodies to the development of clinical nephritis. No other disease states were tested and only one other antigen, rabbit brain, was used as an antigen control. The observation could not be confirmed in 78 patients with scarlet fever studied by Kay and his co-workers.[42]

Some of the quantitative considerations and types of controls necessary to appreciate the problems involved in the detection of autoantibodies have been presented by Osler, Hardy, and Sharp.[43] Serum from approximately 20 per cent of nonsyphilitic normal individuals reacted to fix complement with extracts of human cardiac tissue. A similar percentage of individuals with various diseases, including some with kidney disease, also reacted positively.

A greater incidence of positive reactions was observed in patients with rheumatic fever, syphilis, and chronic biologically false-positive Wassermann reactions. There is no doubt that many febrile and inflammatory diseases are accompanied by the appearance in the circulation of substances, presumably antibodies, which react with extracts of certain normal homologous tissues. Many clinical and experimental diseases may be ascribed to the adjuvant effect of infection on tissues and the production of autoantibodies, as in sympathetic ophthalmia, acquired hemolytic anemia, thrombocytopenic purpura, and experimental encephalomyelitis in monkeys. Whether the reactions observed with serum from patients with nephritis and rheumatic fever represent antigen-antibody reactions, and whether such reactions occur similarly in vivo to produce a diseased state, remains to be proved.

Interesting in vitro studies were conducted by Lippman, Cameron, and Campbell[44] demonstrating that serum from 6 patients with nephritis inhibited

the growth and tubular function of explants of rat kidney and the growth of chick mesonephros, heart, and brain. As controls, serum from 4 normal individuals exhibited no inhibitory effect. The lack of specificity with respect to species and tissue is apparent. The author's interpretation that common antigenic material in the kidney, heart, and brain may provide a rational basis for the clinical association of nephritis, rheumatic carditis, and chorea is untenable in view of the lack of more than chance coexistence of nephritis and the rheumatic diseases. Sera from other febrile illnesses, if tested, might prove to be equally noxious to tissue explants.

It appears unlikely that the antibody would remain in the circulation if it had a pathogenetic affinity for available renal tissue. Of interest in this respect is the work of Hume and his associates.[45] In a study of 9 renal homotransplants in humans, 4 developed measurable function and secreted urine for from 37 to 180 days. Two of these were in patients with chronic glomerulonephritis. The transplanted kidneys did not develop lesions of nephritis as might be anticipated if nephrotoxic substances were circulating. That glomerulonephritis of a special type could develop during the time interval of 37 days was dramatically demonstrated in a kidney transplanted into a patient with periarteritis nodosa. The development of glomerulonephritis in this latter instance may have been due to circulating antibodies or other causes. The lack of it in the 2 patients with pre-existing glomerulonephritis serves to emphasize the difficulties that arise when attempts are made to identify pathogenetic mechanisms with in vitro immunologic phenomena involving complex antigenic material.

A provocative observation relating the possible occurrence of antigen-antibody interaction to acute nephritis was made by Stetson and co-workers.[6] Following infection with type 12 streptococci, 32 patients were given gamma globulin and 108 patients served as placebo-treated controls. A third group of 44 patients received penicillin and had a very low incidence of nephritis. Five of the 32 patients receiving gamma globulin and 5 of the 108 placebo-treated controls developed acute nephritis. In addition, 2 of the gamma globulin group developed "possible" nephritis, while a comparable fraction of the control group, 7 of the 108, developed "possible" nephritis. Although the observed difference in attack rates was not statistically significant, an adverse effect of gamma globulin is suggested by this study. It appeared to the authors that those patients with nephritis who had received gamma globulin were more severely ill and presented more pronounced manifestations of acute nephritis than did those in the untreated group. Perhaps more surprising in this study was the observation that the gamma globulin-treated patients also had definitely enhanced antistreptolysin responses much in excess of the amount of exogenous antistreptolysin contained in the injected gamma globulin. It is possible that the gamma globulin increased the incidence and severity of nephritis by way of a passively induced allergic reaction. However, the additional observation that antistreptolysin titers were also enhanced suggests that all these phenomena may be related to more severe or protracted type 12 infections in this group of patients. The infection may have been more severe as a result of chance vari-

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ation, or actually caused in some unexplained fashion by the action of gamma globulin. It is difficult to suggest alternative interpretations for the enhanced antistreptolysin titer in the gamma globulin-treated group. Gamma globulin with antibody to type 12 streptococci did not appear to result in urinary abnormalities in 20 patients infected with heterologous types of streptococci, heightening the specificity of the presumed allergic reaction. The latter observation may explain, in part, the lack of noticeably deleterious effect on the kidney when antiscarlatinal serum or gamma globulin is used in scarlet fever. In a careful study of the incidence of nephritis following administration of antiscarlatinal serum, Osman[46] noted that it was of no value as a prophylactic against nephritis, but neither was there an increased incidence following the use of the serum. Untoward renal effects following gamma globulin in scarlet fever were not noted in other studies with gamma globulin in streptococcal infection.[47,48]

COMPLEMENT IN NEPHRITIS

The capacity of serum complement (C′) to participate in immune phenomena (Bordet and Gengou) has directed attention to complement fixation as an indicator of the occurrence of an immune reaction. The occurrence of complement fixation in vivo has been described in guinea pig anaphylaxis[49] and in human serum sickness.[50]

With earlier methods for titration of serum complement, many diseases were thought to be associated with a low complement titer, and nephritis was included among them.[51-53] In 1939, Kellett and Thomson[54] employed a 50 per cent hemolytic method and demonstrated a decrease in serum complement early in the course of acute nephritis. They suggested that complement determinations might be of aid in differentiating acute nephritis from exacerbations of chronic nephritis, where no diminution of complement was apparent. Thomson, Arnott, and Matthew[55] were able to differentiate acute glomerulonephritis from toxemia of pregnancy by complement titration. Subsequent work by Reader,[56] Lange and associates,[57] and Fischel and Gajdusek[58] confirmed the finding of a low C′ in acute nephritis. In the latter study, the method employed was a precise and reproducible one, described by Mayer, Osler, Bier, and Heidelberger,[59] in which a spectrophotometric determination of the 50 per cent hemolytic unit was done with optimal quantities of magnesium and calcium. This method permits the establishment of well-defined normal values[60] and the detection of degrees of variation not previously appreciated. Of 18 patients with acute nephritis observed during the first ten days of apparent illness, all but 1 had decidedly low C′ levels, and the one exception could be explained by a coexisting illness. Somewhat more than one-half the patients had a return of C′ to normal levels, or above, by the end of the third week.[58]

Interest in the phenomenon of complement fixation in the test tube, as exemplified by the Wassermann reaction, focused attention on the participation of complement in immune phenomena. It was not generally appreciated that the most frequent variation in complement clinically encountered is an increase in complement associated with inflammation.[60-62] When other conditions known to be associated with high complement levels, occurred together with acute ne-

phritis,[60,61] such as abscesses, penicillin sensitivity, rheumatic fever, and thyrotoxicosis, increases in complement during the course of the nephritis were observed.[58]

The low C′ in acute nephritis is generally viewed as a manifestation of an antigen-antibody reaction in vivo. Ogawa and Sato[63] demonstrated that the onset of nephrotoxic nephritis in rabbits is associated with a fall in serum complement. Schwab and his associates[64] described a similar decrease of C′ in serum sickness in rabbits at the time renal lesions and circulating antibodies appeared.

The fixation of complement in vivo has been studied in our laboratory with Benaceraf and Nordén (unpublished). A rough correlation of complement fixation with the amounts of antibody and antigen uniting was found, as has been described more precisely by Osler and Heidelberger for the in vitro reaction.[65]

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The low C′ in acute nephritis may be ascribed to mechanisms other than fixation of C′ by antigen-antibody reactions. Loss of C′ in the urine has been reported by Seifter and Ecker.[66] However, in other clinical conditions associated with proteinuria no decrease in C′ was observed.[58] The presence of other anticomplementary substances, such as disproportionate quantities of gamma globulin, might result in a low C′,[67] but this does not appear to occur in acute nephritis. Finally, a deficient production of complement may explain the low levels, as has been postulated for certain moribund patients.[58] However, in patients with acute nephritis, complement production up to abnormally high levels is observed under the stimulus of associated or intercurrent inflammatory condition.[58] It would thus appear that the low C′ of acute nephritis is related to a massive and, in some instances, protracted antigen-antibody reaction following a streptococcal infection. However, in certain instances, a low complement persisted after apparent subsidence of acute nephritis.[58]

The value of serum complement in defining an immune process in chronic nephritis, or in the nephrotic syndrome, is less satisfactory. In chronic nephritis an elevation of complement is often found,[54,58] although on occasion it may be strikingly decreased (cf. case 38, ref. 58). In the nephrotic syndrome, titers vary but are generally low.[57,58] Serum complement may be low in conjunction with the pronounced reduction in all the serum proteins. In addition, hemolysis is technically difficult to measure in the presence of markedly lipemic serum. Interpretations of complement titration in nephrosis are correspondingly hazardous.

In conjunction with the studies of experimental nephritis in animals and the epidemiologic studies in man, the study of serum complement appears to lend substance to the hypothesis that acute nephritis is the result of an antigen-antibody reaction. It is possible that chronic nephritis and the nephrotic syndrome may also be the result of an allergic reaction in the kidney, but at present the data are less convincing. Until additional evidence is forthcoming, these latter processes may readily be interpreted as nonallergic sequelae of an initial renal injury.

It is rare to find nephritis associated with infections unrelated to hemolytic streptococci, and studies of a concomitant immune response are limited. In 7 patients with pneumococcal lobar pneumonia who developed acute nephritis,

Seegal[68] noted a latent period of two to three weeks between the initial infection and the onset of nephritis. Glomerulonephritis develops more frequently during the course of subacute bacterial endocarditis. Earle[69] found that patients with subacute bacterial endocarditis, but without renal complications, had elevated complement levels. In contrast, however, patients who had subacute bacterial endocarditis complicated by focal or diffuse glomerulonephritis had decidedly low complement levels, again suggesting the possibility of an antigen-antibody reaction. The transient nephritis of serum sickness may be related to a similar mechanism.

SUMMARY

Clinical and serologic data concerning immune responses in human glomerulonephritis are reviewed. The latent period of acute nephritis and the accelerated latent period of chronic nephritis following hemolytic streptococcal infection suggest the occurrence of an immune reaction to the infection. Other clinical data are less impressive. Serologic studies are considered in two groups: those which pertain to the preceding streptococcal infection and those thought to indicate an allergic reaction in nephritis.

Except for the type-specific antibodies, patients who develop nephritis after a streptococcal infection exhibit little difference in the magnitude and character of their antibody response to most antigens of the streptococcus. Circulating autoantibodies and nephrotoxic agents may be demonstrated in nephritis and in various other conditions. In the absence of adequate controlled studies, they do not appear to be a unique or pathogenetic factor for the development of acute nephritis.

In conjunction with epidemiologic data and studies on experimental nephritis, evidence derived from the study of serum complement suggests that acute glomerulonephritis is the result of an antigen-antibody reaction. This hypothesis is not incompatible with the view that a direct toxin may also affect the kidney. Data for chronic nephritis and nephrosis are less convincing. Although the possibility of an allergic reaction is not excluded, other pathogenetic mechanisms require consideration as causes of the chronic forms of kidney disease.

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THE DIFFERENTIAL DIAGNOSIS OF ACUTE AND CHRONIC GLOMERULONEPHRITIS

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THE differential diagnosis of acute glomerulonephritis can be simple or complex in proportion to our familiarity with the atypical forms of the disease (Fig. 1). Few physicians will fail to recognize the patient who, one to four weeks after a hemolytic streptococcal infection, reports the onset of pallor, puffy face, periorbital swelling, abdominal pain, and coffee-colored urine, and is found on examination to have hypertension, proteinuria, hematuria, and blood casts. Only a few diseases need be considered in such a syndrome. However, a much broader listing is entailed when the physician seeks out the subtle, the masquerading, or the atypical forms of acute glomerulonephritis.[1] A number of diseases worthy of consideration in this differential diagnosis are discussed below.

Of no less importance is the demanding task of deciding what is *not* glomerulonephritis when one is presented with incomplete or undocumented histories, inconclusive reports from insurance, employment, or military service examinations, vague symptomatology, conflicting laboratory reports, or incidental findings on routine urinalyses. Reassuring words must necessarily come with difficulty when one projects the possible long-term implications of diffuse glomerulonephritis. We have found this a particularly pointed problem when dealing with fellow physicians, nurses, and scientists who suspect that they, their children, or their relatives may have this disease. We have encountered severe psychologic reactions in medical personnel and presumably well-informed patients. Such reactions have ranged from acute panic and total preoccupation to frank psychosis and, in one instance, suicide, from dwelling overlong on the disease. These are compelling reasons for a full and correct evaluation of the patient who is suspected of having glomerulonephritis. Essential to such an

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evaluation is a consideration of the differential diagnosis. This in turn will depend somewhat on one's clinical concept of the disease. We regard it as a clinical spectrum graded from the mild cases with urinary findings alone to the more severe with edema, hypertension, azotemia, and, in unusual cases, severe oliguria. The detailed clinical and laboratory features are discussed elsewhere in this symposium and are re-emphasized here only in so far as they help to separate acute glomerulonephritis from the following disease processes which should be considered in the differential diagnosis.

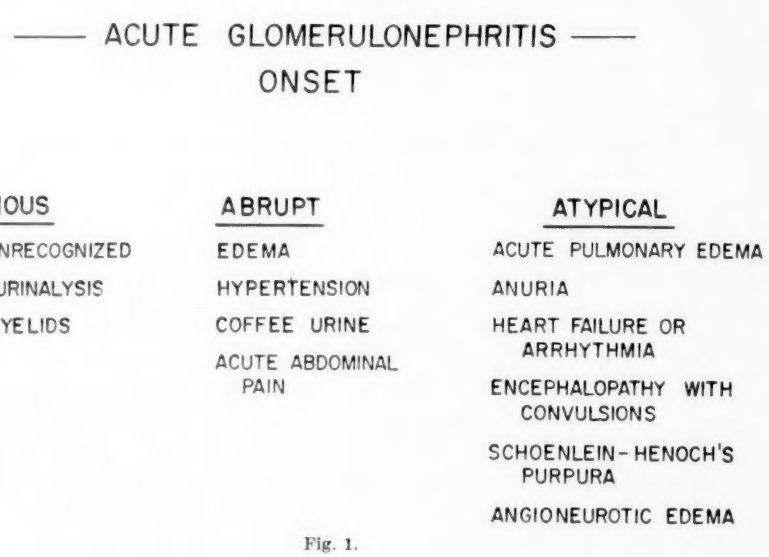

Fig. 1.

Exacerbation of Chronic Glomerulonephritis.—The clinical and urinary findings of an exacerbation occurring in the course of chronic glomerulonephritis may be indistinguishable from those of classical acute glomerulonephritis. The distinction is critical since every case of latent or chronic glomerulonephritis which is incorrectly included in a series of acute glomerulonephritis weights the statistics on prognosis. Such errors may account for part of the difference between figures on prognosis cited for different age groups. There is no substitute in this differential diagnosis for meticulous perusal of previous medical records, the charts from all hospitalizations, evidence during tonsillectomy or tooth extractions, reports of medical checkups, and records of the family doctor, insurance, employment, selective service, military, and separation examinations. Often an invaluable clue suggesting prior renal disease is contained in such material. Other helpful points in favor of chronic nephritis are a history of antecedent edema, periorbital swelling, chronic retinal changes, the finding early in the present course of hypoproteinemia and albuminuria of significant proportions, or a history of an antecedent nephrotic syndrome. The latent period between the infection and signs of clinical nephritis is much shorter in the exacerbation than in acute nephritis. Any increase in antistreptolysin titer will, therefore, be more likely to follow rather than precede clinical signs. In the chronic state,

advanced retinal vascular changes, anemia, and urochrome pigmentation of the skin are frequently present. Loss of concentrating power is more pronounced, and renal failure casts are valuable in distinguishing the chronic form of the disease.

Convalescence From Hemolytic Streptococcal Infections.—Recurrence of sore throat, persistent cervical lymphadenopathy, low-grade fever, headache, nausea and vomiting, lethargy, anorexia, and circles or puffiness under the eyes may mean delayed convalescence, recurrence of the original infection, or may herald the onset of clinical acute glomerulonephritis. Important diagnostic aids include frequent examination of fresh urinary sediments, continued increase in the sedimentation rate after fever subsides, and decreased serum complement.

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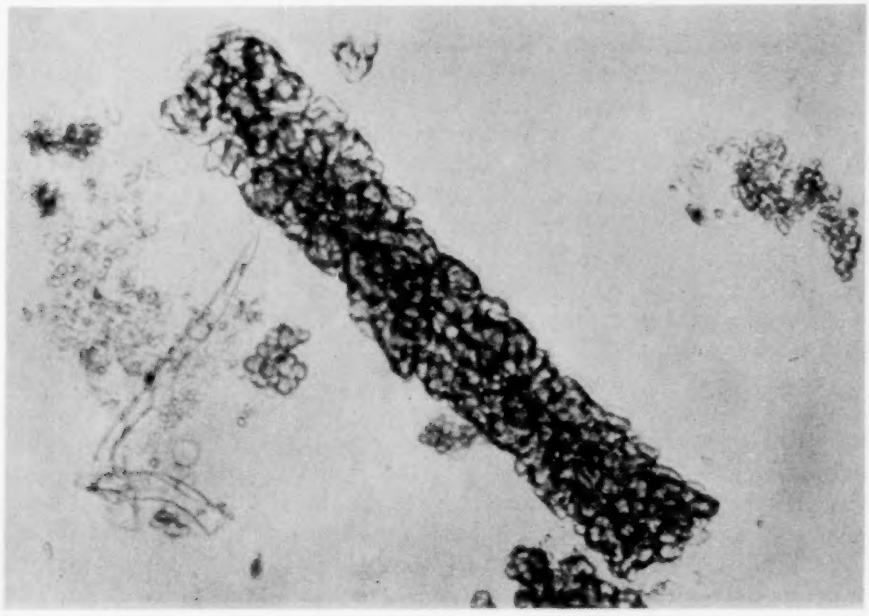

Fig. 2.—Typical blood cast from the urine of a 5-year-old boy in the first week of acute diffuse hemorrhagic glomerulonephritis. There is a hyaline matrix with several hundred red blood cells and long filaments of fibrin constituting a true blood cast. Photographed in wet specimen without stain.

Unanswered is the critical question of whether isolated microscopic hematuria or abnormal Addis counts should, in fact, be considered a subclinical form of the disease. If so, it is much more common than supposed. Kempe, Olmsted, and Curnen[2] found 20 instances of microscopic hematuria in 80 children; 4 had other clinical signs of nephritis. Siegel, Rammelkamp, and Griffeath[3] studied a streptococcal epidemic involving 131 children; 2 had clinical glomerulonephritis, 2 had gross hematuria, and 27 had microscopic hematuria. Lyttle[4] followed Addis counts in 14 males (aged 4 to 14 years) for eight to forty-five days after scarlet fever. All showed transient increases in urinary protein, cells, and casts.

We cannot be dogmatic as to whether or not these represent instances of mild acute glomerulonephritis. There is urgent need for a series of renal biopsies in such patients in whom urinary findings have been carefully documented. It cannot be overemphasized that the study of *urinary sediment is the greatest single aid in this situation.*[5] The finding of typical blood casts (Fig. 2) is most helpful. Serial examinations of freshly voided urine, multiple concentrations of the sediment, acidification of alkaline urine, addition of salt to hypotonic urine, and special stains should be used as indicated.

Proteinuria—Febrile.—Proteinuria occurs in many infectious diseases and has been explained on the basis of increased permeability of glomerular capillaries, acute glomerulitis, or focal glomerulonephritis. Proteinuria has been experimentally produced in humans by artificially raising body temperature in a Kettering hypertherm.[6] An analysis of 300 febrile patients, on the other hand, revealed that bacterial pneumonia and influenza were disproportionately frequent in producing this condition.[7] It is therefore debatable whether the proteinuria is due to a toxin or to the fever per se.

The important clinical differential from acute glomerulonephritis lies in the absence of a latent period between the onset of infection and the onset of the urinary findings. The nature of the infection need not be of streptococcal origin. Febrile proteinuria characteristically occurs at the height of the initial infection and is usually less than 0.5 Gm. per twenty-four hours. Urinary sediment findings are usually sparse, and the rare casts are not apt to include inflammatory elements such as red cell and leukocyte inclusions. Edema and other constitutional signs of nephritis are absent.

Proteinuria—Postural (*"Orthostatic," "Lordotic," "Constitutional"*).—A posture-sensitive proteinuria has been reported in from 2 to 30 per cent of young people. Such studies have been carried out on a large scale in draftees, military units, camps, school populations, etc. Unfortunately, the results are only of limited interest. While objectivity exists on the positive side (i.e., demonstration of a postural effect), we must reject negative claims for the absence of all renal disease based on one or two normal urinalyses. Many experienced clinicians have seen postural effects in the proteinuria of known cases of glomerulonephritis or have followed an individual with "postural" proteinuria for years only to be confronted later with the stigmata of chronic glomerulonephritis. It is said that red cells, epithelial cells, and casts may be seen with postural proteinuria, but without a biopsy the absence of latent glomerulonephritis cannot be proved.

In general, the diagnosis of postural proteinuria is probable when the horizontal urine is normal, the vertical abnormal, and a full renal evaluation is negative. The quantity of protein is usually small (less than 1.0 Gm. per day when measured on a twelve to twenty-four hour urine; most larger figures have been obtained by extrapolation from the first fractional collection). The condition may be associated with thin, pale, delicate body types, with postural defects, scoliosis, muscular hypotonia, neurocirculatory asthenia, lordosis, protuberant abdomen, or with the presence of a varicocele.

Focal Glomerulonephritis.—The best-known form is *focal necrotizing (embolic) glomerulonephritis*, which is present in a significant percentage of patients with

bacterial endocarditis lasting six weeks or more. Bell[40] has reported the lesion in 2.9 per cent of patients with rheumatic endocarditis; 7.1 per cent of patients with acute primary endocarditis; 5.8 per cent of patients with secondary endocarditis, and in 53 per cent of patients with typical subacute bacterial endocarditis. Allen[41] regards the focal renal lesion as virtually diagnostic of subacute bacterial endocarditis. However, both the pathologic and many of the clinical findings of S.B.E. (sepsis, anemia, splenomegaly, infarcts, and renal disease) have been described in other diseases such as Wegener's granulomatosis.[8] Clinically focal glomerulonephritis can present most of the signs and all of the urinary findings of acute glomerulonephritis. Hypertension and edema are, however, quite rare and uremia is uncommon except in extremely widespread lesions. The finding of a telescoped urinary sediment[9,10] (Table I) may be helpful. The

TABLE I. URINE SEDIMENT FROM THE SEPARATE STAGES OF GLOMERULONEPHRITIS

Acute	*Nephrotic Syndrome*	*Chronic*
Red cells	Massive proteinuria	Less proteinuria
Hyaline casts with red cell inclusions	Hyaline casts	Pigmented granular casts
Blood casts	Cellular casts, vacuoles	Waxy casts
Positive benzidine	Oval fat bodies	Broad, renal failure casts
	Doubly refractile fat bodies	

is telescoped in

1. Collagen kidney—periarteritis nodosa, lupus erythematosus, progressive systemic sclerosis (scleroderma), viscerocutaneous collagenosis
2. Focal necrotizing glomerulonephritis (subacute bacterial endocarditis)
3. Rare cases in which exacerbation of chronic glomerulonephritis occurs in the presence of the nephrotic syndrome[9]

differential diagnosis is best made by the finding of other signs of subacute bacterial endocarditis such as a positive blood culture, anemia, heart murmurs, splenomegaly, embolization, bacteriuria, the character of the urinary sediment, and the absence of hypertension. The focal lesion must be differentiated from other renal complications of subacute bacterial endocarditis such as renal infarcts and acute diffuse glomerulonephritis.[11] Sometimes, however, renal biopsy

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may be a diagnostic necessity or an aid in confirming the value of embarking on a long course of penicillin therapy. This is illustrated by the following case:

CASE 1.—A 63-year-old white man was admitted with a tentative diagnosis of subacute glomerulonephritis. He had been in good health until two years prior to admission when he had high fever, shaking chills, and an upper respiratory infection treated with penicillin for four days The symptoms, together with frank hemoptysis, recurred in one month and the patient's illness was diagnosed as the Guillain-Barré syndrome. Complete recovery occurred. Neither proteinuria nor hypertension was noted. One month prior to the present admission he had a respiratory infection, diagnosed as "influenza," which was marked by fever, chills, fatigue, back pain, and flank pain on the left. Twelve days prior to admission he noted gross hematuria; an examination revealed transitory hypertension, low-grade fever, severe anemia, generalized lymphadenopathy, proteinuria, and a progressively increasing azotemia. There was a grade III blowing systolic murmur at the apex. The liver was palpable and the kidneys were tender to palpation. The urine specific gravity was 1.010, with 4 plus protein and a pH of 4.5. The sediment was loaded with red cells, and with granular, broad renal failure and red cell casts. Doubly refractile fat bodies were seen. Quantitative protein excretion was 1.4 Gm. in twenty-four hours. The blood urea was 154 mg. per cent, total proteins were 7.0, albumin 2.4, and globulin 4.6 Gm. per cent.

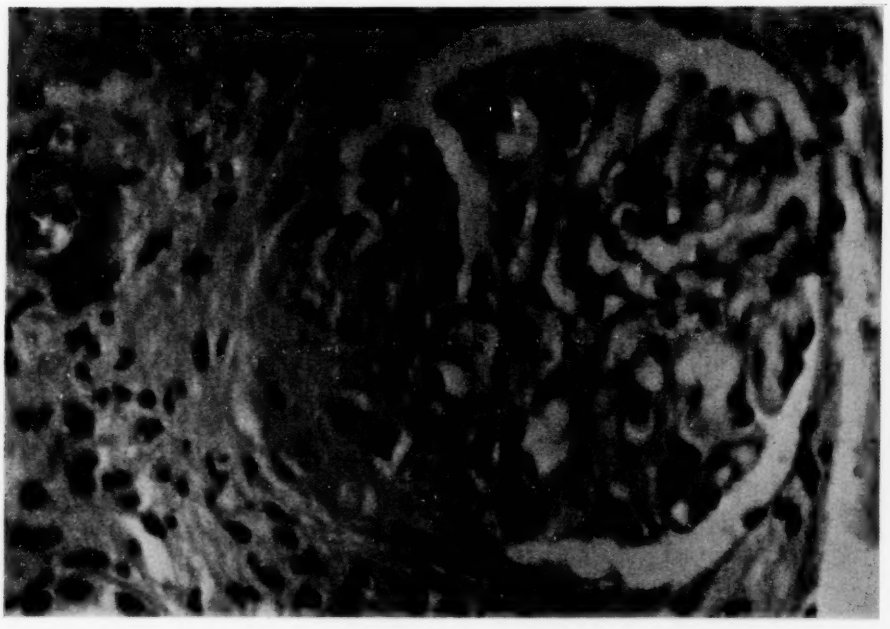

Fig. 3.—Patient 1. Glomerulus shows fibrinoid degeneration of collagen localized to one segment of the glomerular tuft with adhesion to Bowman's capsule, which shows some proliferation and fibrosis. Interpretation: Focal necrotizing glomerulonephritis of subacute bacterial endocarditis. (Magnification ×440; reduced ¼.)

Search for the lupus cell phenomenon, repeated blood and urine cultures, Brucella and febrile agglutinins were negative. A renal biopsy confirmed the diagnosis of focal necrotizing glomerulonephritis (Fig. 3) and the patient was adequately treated with penicillin. His blood urea decreased from 151 to 65 mg. per cent and he was discharged on the fortieth hospital day. He died some months later from a cerebral hemorrhage.

Focal suppurative glomerulonephritis: This disease is produced by direct action of bacteria on glomerular capillaries. This lesion has been described in bacterial endocarditis by Christian[42] and has been assigned considerable importance by Fishberg,[12] who has collected cases following tonsillitis, erysipelas and other skin infections, pneumococcal pneumonia, typhoid fever, measles, meningitis, influenza, malaria and relapsing fever. We believe that this lesion should be considered a manifestation of infection and is closely related to or indistinguishable from miliary abscesses or hematogenous pyelonephritis. It occurs at the peak of the associated disease without a latent period, and urinary findings tend to increase or decrease with the fever and degree of sepsis. Appropriate pathogenic bacteria singly or in clumps are frequently found in the urine. Glitter cells are usually present and bacteria may sometimes be identified in casts by supravital stains or phase-contrast microscopy. Glomeruli show focal endothelial thickening and local leukocytic infiltration. The focal lesions may be seen in glomeruli distant from hematogenous abscesses. Arterioles are normal.

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Focal nonsuppurative glomerulonephritis: This is a controversial classification involving proliferative, exudative, necrotizing, hemorrhagic, or combined lesions localized to one portion of the glomerular tuft. It has been described in association with many chemical nephrotoxins such as arsenic and sulfa drugs and is a particularly common accompaniment of the acute renal insufficiency due to mercury. It has also been described with allergic arteritis, rheumatic fever, and a variety of bacterial and fungus diseases.

Some investigators would prefer to eliminate these subclassifications and refer simply to focal glomerulonephritis, specifying the etiology where it is known. Differentiation may be difficult between the diffuse acute glomerulonephritis seen with *Streptococcus viridans* endocarditis and the focal lesion described in this section, since the two may coexist. The focal lesion, as with all the focal diseases mentioned above, produces an episodic urinary sediment and is less apt to produce renal failure, hypertension, and uremia unless a large share of the glomerular population is affected. Renal biopsy should be helpful in the delineation of these poorly understood focal diseases.

Acute Pyelonephritis.—Acute pyelonephritis may be difficult to distinguish from those cases of acute glomerulonephritis characterized by a septic course with fever, chills, and headache. Barring coexistence of the two diseases, or persistence in a patient with acute glomerulonephritis of a septic focus (peritonsillar abscess, cervical adenitis, otitis, mastoiditis, skin abscess, sinusitis, or osteomyelitis), uncomplicated acute pyelonephritis can usually be differentiated from acute glomerulonephritis by the persistently febrile course, characteristic urinary findings of bacteriuria, pyuria with or without clumps of leukocytes, and "glitter" cells observed under reduced light with an ordinary microscope, phase contrast microscopy, or Sternheimer-Malbin supravital stain.[13,14] Proper use of the gram-stained smear and quantitative colony counts on urine cultures help greatly in the separation of true bacteriuria from bacterial contamination of bladder or voided urine. Periorbital edema is uncommon in pyelonephritis and the nephrotic syndrome is virtually nonexistent. Additional circumstantial evidence may exist in the demonstration of gram-negative bacteremia, meta-

static infection in liver, lungs, skin, or brain, or the finding of an additional basis for renal infection such as congenital anomalies, obstructive uropathy, or hypogammaglobulinemia.

It should be emphasized that pyelonephritis is a common cause of microscopic and even gross hematuria. Necrotizing papillitis of varying degree may furnish sloughed renal epithelial cells and doubly refractile fat bodies in addition to hematuria and may be present with a rapid onset of oliguria or anuria. We have demonstrated papillitis by renal biopsy in one individual who had a sudden onset of gross hematuria, followed by brown urine, anuria, edema, hypertension, and uremia, an onset virtually impossible to distinguish clinically from acute glomerulonephritis.

Fig. 4.—The patient was a 47-year-old Negro man with staphylococcal gastroenteritis and myocardial infarction. Proteinuria was 8 Gm. per day with many doubly refractile fat bodies and fatty and hyaline casts in the urine. Blood urea nitrogen was 6 mg. per cent. Fifteen glomeruli seen on renal biopsy showed focal increase in glomerular cellularity, thickening of basement membrane, fibrinoid degeneration, adhesions, and fibrosis. There were areas of interstitial infiltration with leukocytes, eosinophils, and lymphocytes. Interpretation: Focal glomerulonephritis with mild interstitial nephritis. (Magnification ×500; reduced ¼.)

Tests of renal function performed a few days after onset are apt to reflect the predominantly tubular involvement of pyelonephritis, while the typical patient with acute glomerulonephritis has diminished filtration rate, oliguria, and azotemia in the presence of a disproportionately good concentrating capacity and tubular excretory capacity.

Acute Interstitial Nephritis.—Acute interstitial nephritis is an uncommon disease characterized by diffuse infiltration throughout the kidney, predominantly in the cortex, with polymorphonuclear leukocytes, histiocytes, eosinophils,

and plasma cells. It occurs in the renal reaction to sulfonamides and in a variety of infections. It has been considered as a fulminating, diffuse version of the focal nephritides considered under the heading "Focal Glomerulonephritis," or as a variant of pyelonephritis. The clinical course is usually septic and is frequently fatal. It may be marked by severe oliguria, uremia, and hypertension. Diagnosis rests on the identification of the underlying or associated disease process which usually coexists with or causes interstitial nephritis. The varied nature of the cells in the infiltrate is best demonstrated by the identification of polymorphonuclear leukocytes, band forms, and histiocytes within hyaline casts by the use of supravital stains on fresh urine. The sediment may be both hemorrhagic and inflammatory. Renal biopsy (Fig. 4) may uncover less advanced forms of the disease, our knowledge of which in the past has been largely confined to the rapidly fatal forms, with diagnosis made at autopsy.

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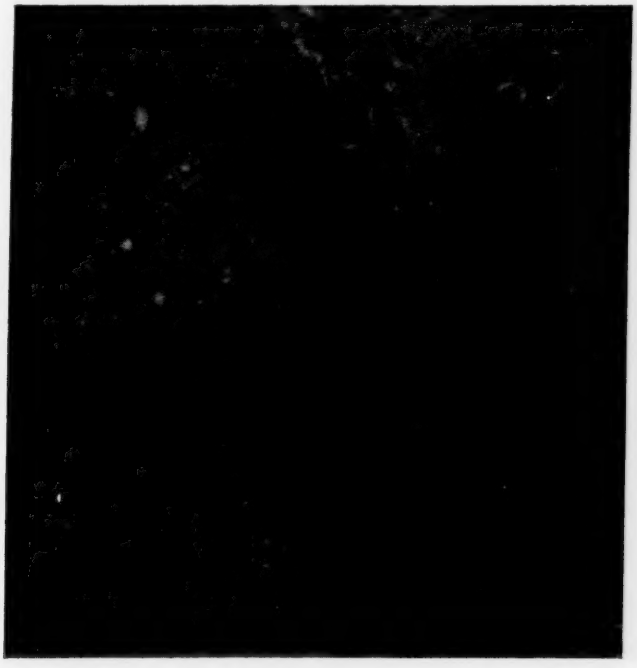

Fig. 5.—Fresh epithelial cell cast from the urine of a 9-year-old boy emerging from the oliguric phase of acute glomerulonephritis. The tubular epithelial cells in the central, convoluted portion of the cast show round form and distinct cell outline. They merge into coarsely granular material in the dilated ends. The size of an attached red cell may be compared. (Light methyl blue ×860.)

Nephrotic Syndrome With Hematuria.—Acute glomerulonephritis on rare occasion may be difficult to distinguish from the nephrotic syndrome, which is characterized by edema, massive proteinuria, hyperlipemia, and hypoalbuminemia. When the nephrotic syndrome occurs as a phase of subacute or early chronic glomerulonephritis, red cells and red cell casts may be found in the urine. It is important to distinguish the nephrotic syndrome with a mixed picture of nephritis (already chronic) from true instances of acute or subacute glomerulo-

nephritis with a nephrotic component. This confusion has undoubtedly introduced considerable error into the statistics on prognosis. Even the relatively pure "lipoid nephrosis" of children, when combined with a superimposed pyelonephritis or lower urinary tract cause for hematuria, may be mistaken for genuine acute glomerulonephritis. Quantitative protein excretions in excess of 4 Gm. per twenty-four hours, hypercholesterolemia, a shift toward the larger lipoprotein fractions in the ultracentrifuge pattern, marked decrease in serum albumin, and the presence of many doubly refractile fat bodies in the urine[15] are all helpful in suggesting the nephrotic syndrome. Only renal biopsy, however, is diagnostically definitive.

It should be mentioned that some rare cases of genuine acute glomerulonephritis have a nephrotic component in the acute hemorrhagic phase which usually subsides *pari passu* with the inflammatory stage. Case 2 summarizes the clinical features of an instance of this combination proved by biopsy.

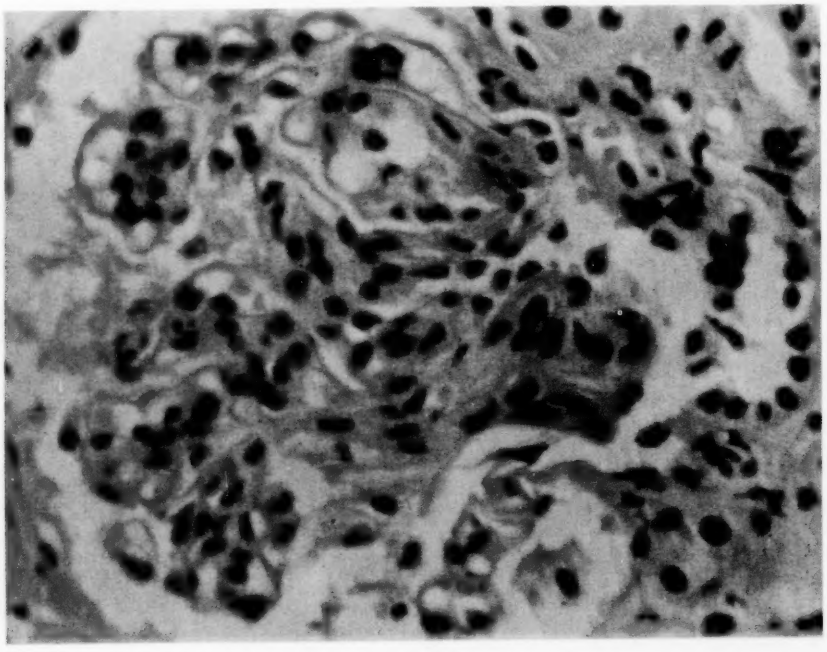

Fig. 6.—Patient 2. Ten glomeruli appeared on renal biopsy, which shows coagulated protein material in Bowman's space. There are focal areas of cellular proliferation and diffuse thickening of the capillary basement membranes and tufts. Some glomerular loops show leukocyte infiltration. Interpretation: Acute diffuse glomerulonephritis, subsiding. (Magnification ×550; reduced ¼.)

CASE 2.—A 14-year-old white boy was admitted because of increasing uremia and oliguria. Urinalyses at the ages of 2, 4, 6, 7, 8, and 11 years revealed from 0 to 4-6 white blood cells per high power field and a trace of protein on one test. He had repeated sore throats, postnasal drip, and allergic urticaria. One year prior to admission he had pharyngitis and scarlet fever complicated by a pneumonitis. Several urinalyses done in the convalescent period were said to be negative. Six weeks prior to admission he had rhinitis followed successively by pharyngitis, lethargy, drowsiness, nausea, vomiting, and periorbital edema. On examination, he had edema

of face and eyelids, retinal edema, and a marked pharyngitis. The urine showed proteinuria, 10 to 15 red blood cells and 5 to 10 white blood cells per high power field, hyaline casts with granular, red cell, and renal epithelial cell inclusions. The Addis count revealed 444,000 casts, 62,000,000 red cells, and 23,000,000 white and epithelial cells per twelve hours, and the protein excretion was 2.4 Gm. per twenty-four hours. With continuing oliguria, the blood urea rose from 91 mg. per cent on admission to 120 mg. per cent before effective diuresis. The throat culture did not reveal beta hemolytic streptococci, but the antistreptolysin titer was 320 units (normal maximum 160), decreasing to 80 in two weeks. The serum cholesterol was 300 mg. per cent. Total serum proteins were 5.5 Gm. per cent with an albumin-globulin ratio of 2.2/3.3. The phenolsulfonphthalein test after diuresis showed 30 per cent excretion in fifteen minutes and the search for LE cells revealed none. The right maxillary sinus showed thickened mucosa; chest x-ray and intravenous pyelogram were normal.

Course.—The patient remained afebrile and the highest blood pressure recorded was 142/98 mm. Hg. Despite previous severe oliguria, his first day's measured urine volume was 1,400 ml. and he gradually developed a diuretic phase up to 5 liters per day with a 22-pound weight loss. The urine sediment was filled with epithelial cells and epithelial cell casts (Fig. 5) during this period. The blood urea nitrogen and cholesterol decreased to normal, but the total serum protein remained depressed at 4.2 Gm. per cent on the seventeenth hospital day. A renal biopsy on the eighteenth hospital day was characteristic of acute glomerulonephritis (Fig. 6). He was discharged from the hospital, and at the present writing (two months later) he has no proteinuria, and rare casts. Microscopic hematuria persists and the sedimentation rate (Wintrobe) has progressively decreased to 12 mm. per hour.

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Pre-eclampsia.—Pre-eclampsia is used here in the restricted sense excluding the aggravation by pregnancy of essential hypertension, chronic pyelonephritis, and the whole gamut of organic renal diseases. The specific renal lesion consists of membranous glomerulonephritis, glomerular hypercellularity, focal adhesions, wire-loop formation and arteriolar thickening. Many of the clinical and urinary findings of acute glomerulonephritis can be duplicated. Differential diagnosis is based on the natural course of the disease during the latter part of pregnancy, the absence of beta hemolytic streptococci in the throat, or changes in antistreptolysin titer and serum complement, together with the well-known observation that true acute glomerulonephritis is extremely rare in pregnancy. Pre-eclampsia is most common in the young primipara. The clinical and urinary findings usually subside within four to six weeks post partum. In one series,[16] only 4 of 154 patients had proteinuria three weeks after delivery.

Necrotizing Arteritis.—Necrotizing arteritis is defined as the accelerated vascular degenerative lesion which is characterized by intimal thickening, fibroblastic proliferation, lamination of collagen, fibrinoid necrosis, intramural hemorrhage, and perivascular inflammatory reaction. This lesion is seen in varying degrees in malignant hypertension, (primary or secondary to pyelonephritis and glomerulonephritis), periarteritis nodosa, systemic lupus erythematosus, and vascular sensitivity reactions to antibiotics, vaccines, and sera. Apresoline has been implicated in some hypertensive patients.

This condition can present a clinical picture not unlike that of acute glomerulonephritis, characterized by rapidly rising diastolic pressure, retinal edema, hematuria, proteinuria, cylindruria, sloughing of renal tubular cells, and doubly refractile fat bodies. It is the only common condition outside of the nephrotic syndrome which leads to protein excretion in excess of 6 Gm. per twenty-four hours.

The clinical differential lies in the age of onset, which is in the fourth to sixth decade (relatively uncommon years for acute glomerulonephritis), the history of antecedent hypertension, the rapid development of retinopathy progressing to papilledema, the lack of associated streptococcal infection with all its clinical and laboratory features, or historical evidence of the administration of causative substances.

Acute Congestive Heart Failure.—Acute congestive heart failure may superficially resemble acute glomerulonephritis. The semblance is most striking in young patients with rheumatic or idiopathic myocarditis. Hematuria, renal epithelial cells, and casts may occur with multiple renal infarctions from emboli—the most common cause of which is an active rheumatic auriculitis. The differential from active rheumatic myocarditis is best brought out by considering the biologic differences of glomerulonephritis and rheumatic fever.[17] Points favoring the diagnosis of acute congestive heart failure are: identification of the underlying heart disease, an enlarged or dilated heart, increased venous pressure, prolonged circulation time, or ventricular gallop rhythm well in advance of hypertension or nephritic urinary findings. The edema is usually gravitational in distribution, and mobile. Hepatomegaly is common in congestive failure. Urine sediment abnormalities are apt to be episodic in character if due to multiple embolization. Splenic or unilateral renal tenderness are common under the latter circumstances.

Other Glomerular Diseases.—Other glomerular diseases may be mentioned in passing. They include *fulminating* forms of intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease), amyloid disease, and uric acid nephritis.

An acute benign disease called "Nephropathia Epidemica" has been described in Scandinavia by Zetterholm,[18] Myhrman,[19] and others.[20] It is marked by malaise, fever, vomiting, acute abdominal pain, and occasional albuminuria and isosthenuria. Hypertension, red cell casts, and residual lesions are absent. The disease has a rapid, benign course. Etiology is unknown.

Radiation nephritis[21] may occur in acute or chronic form and its clinical and laboratory features may resemble those of glomerulonephritis. A history of exposure of the lumbar area to high dosages of x-rays or radium is the usual clue to this possibility.

Syphilitic nephritis and nephrosis[22-24] are very uncommon but may be distinguished by their association with active, usually secondary, syphilis and their prompt response to antibiotic therapy.

Proteinuria and other features of acute glomerulonephritis have been described in yellow fever. Both glomerular and tubular lesions have been reported. Pheochromocytoma may present with a combined renal and hypertensive picture resembling acute glomerulonephritis.[26] In addition to the usual diagnostic tests for pheochromocytoma, such as lowering of the blood pressure with adrenergic blocking agents, a clue to the diagnosis may be gained from a cyclic waxing and waning of proteinuria and abnormal urinary sediment along with the hypertension.

Epidemic hemorrhagic fever,[27] a disease which received considerable investigative attention during the Korean War, may present with a fulminating picture of proteinuria, hematuria, oliguria, and generalized hemorrhagic phenomena. Fortunately, the disease has not obtained a foothold in this country.

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DIFFERENTIAL DIAGNOSIS OF CHRONIC GLOMERULONEPHRITIS

On all too rare occasions, the physician may be presented with a patient who has a good history of acute glomerulonephritis, a documented nephrotic syndrome, or proteinuria of long standing. When he examines such a patient and finds edema, hypertension, stigmata of the general uremic syndrome, progressive failure of glomerular or tubular function, proteinuria, hematuria, or cylindruria, a correct diagnosis of chronic glomerulonephritis will usually be achieved. Without such history, undiagnosed cases of chronic glomerulonephritis are usually seen in their early, terminal, fragmentary, atypical, subacute, recurrent, latent, or malignant forms. The differential diagnosis must then include virtually the entire classification of organic renal disease and the functional proteinurias.

Any of the acute conditions discussed in the first part of this paper, when they present with a less fulminating clinical picture or when they persist for many weeks, may merge in a gradual and continuous clinical spectrum with many of the features of chronic glomerulonephritis. The following chronic diseases should be considered in the differential diagnosis.

Chronic "Nephrosis".—The existence of a genuine chronic nephrosis (lipoid nephrosis) has been hotly debated since the introduction of the concept by Muller, Munk, Volhard, and Fahr. The entity has been stoutly defended by Fishberg.[28] However, in much of the older literature the diagnosis has been made on patients who had definitive causes for a nephrotic syndrome, who had simply a prolonged nephrotic syndrome without evident glomerular insufficiency, or on children who were autopsied during an active nephrotic syndrome. Certainly many of these cases could have been in the nephrotic stage of glomerulonephritis or suffering from one of the more recently described causes of the nephrotic syndrome. The histologic criteria of membranous glomerulonephritis and absence of proliferation or fibrosis are difficult when applied to pediatric material. What is seen in the childhood kidney may be an episode out of a lengthy pathogenesis interrupted by death. Any purely clinical diagnosis of "pure" lipoid nephrosis is debatable. Neither the duration of the nephrotic syndrome nor the absence of renal failure rules out glomerulonephritis. We have biopsied a patient (aged 30) who had a nephrotic syndrome for nine years and found crescents, fibrosis, and unequivocal glomerulonephritis. That nephrotic syndromes of undetermined etiology do exist, no one can deny. But in our experience, exhaustive search for a cause, improved diagnostic techniques and in particular, the use of renal biopsy, can whittle down enormously the size of this group. The nephrotic syndrome is seen in typical (secondary) and atypical (primary) amyloidosis, multiple myeloma, intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease), progressive systemic sclerosis (scleroderma) even without skin changes, renal infarction, thrombosis of renal veins, syphilis, systemic lupus erythematosus, periarteritis nodosa, chronic exposure to nephrotoxins such as carbon tetrachloride and heavy metals, and in reactions to Tridione and poison oak.

We have observed patients in whom a cause for the nephrotic syndrome remained unknown until it was demonstrated that there had been a prodromal exposure to carbon tetrachloride or trichlorethylene. In one of the oldest living

patients (39 years) with sickle cell anemia, a nephrotic syndrome recently developed. Renal biopsy shows nephrosclerosis and miliary infarctions of the renal cortex. Biopsies of patients with pre-eclampsia may show diffuse thickening of the basement membrane, focal adhesions between capillary tuft and Bowman's capsule, and tubular degeneration, a picture difficult to distinguish from the "membranous glomerulonephritis" described as classical for chronic nephrosis, or lipoid nephrosis. We have one patient with proteinuria, fat bodies, hypercholesterolemia, recurrent edema, and mild hypertension, which have apparently persisted unchanged over several years. Twenty years ago, during her last pregnancy, she had pre-eclampsia. Can the vascular and renal results of this lesion persist with neither resolution nor evolution?

The criteria for the diagnosis of chronic or "pure" nephrosis, therefore, should be rigid and should exclude the known causes of the nephrotic syndrome, histologic demonstration of membranous glomerulonephritis with the absence of proliferative or degenerative changes in the glomeruli, and reasonable passage of time for the evolution of the lesions of glomerulonephritis if they are to occur. In the present state of our knowledge, we believe the interests of both patient and science would be better served by classifying most of such cases, after eliminating other etiologies, as nephrotic syndrome, cause undetermined.

Chronic Pyelonephritis.—Chronic pyelonephritis is a largely undiagnosed, chronic disease with protean clinical manifestations[29] which may resemble chronic glomerulonephritis. Our view of this disease has been gradually enlarging since the excellent monograph of Weiss and Parker[30] effectively tied together for the clinician the "pyelitis" of the pediatrician, the "toxemia" of the obstetrician, the "pyuria" of the urologist, and the hypertensive disease seen by the internist. In fact, chronic pyelonephritis may deserve a place as a great imitator. We have been able to identify 20 clinical syndromes presented by this disease.[31]

In its more commonly recognized septic form, chronic pyelonephritis can be differentiated from chronic glomerulonephritis by considering history, symptoms, and laboratory findings. One searches for the predisposing conditions for ascending, hematogenous, or lymphogenous spread of infection, associated congenital genitourinary anomalies, and calculus or obstructive uropathy. Fever during pregnancy, urologic instrumentation, and knowledge of multiple or indwelling catheterization are important material facts. Chills, fever, malaise, abdominal pain, costovertebral angle tenderness, and reflex ileus are all more common in pyelonephritis than in glomerulonephritis, as are the symptoms of the frequently associated cystitis such as frequency, dysuria, urinary tenesmus, and a feeling of suprapubic pressure. The kidneys and ureters may be tender on palpation. Metastatic abscesses in lungs, liver, skin, or brain may suggest the kidney as the focus for the bacteremia. Perinephric and subdiaphragmatic abscesses are occasionally seen. Leukocytosis, bacteriuria, pyuria, identification of pathogenic bacteria in urine, glitter cells, and abnormalities in the intravenous pyelogram are all helpful laboratory findings. In the less active, silent, and advanced types of pyelonephritis, abnormalities of tubular function are apt to be more prominent than in chronic glomerulonephritis and protein excretion tends to be less (less than 1 Gm. per day) and, indeed, may be absent.

For a given degree of renal failure, the patient with pyelonephritis is less apt to have marked diminution in serum total protein and albumin, and hyperlipemia is unusual save in those patients with associated diabetes. Many patients with chronic pyelonephritis have a low-grade normocytic normochromic anemia (hematocrit 32-38) even in the absence of significant azotemia, whereas those with chronic glomerulonephritis often are not anemic until they develop the hemolytic anemia of uremia. Patients with pyelonephritis generally have fewer casts in serial urines and rarely have doubly refractile fat bodies, although both fat bodies and epithelial cell casts in all stages may be seen following infarcts or active necrosis of tubular tissue. Such infarcts are a common part of the pathology of pyelonephritis. Broad renal failure casts are seen in the late stages of both pyelonephritis and glomerulonephritis.

Edema in pyelonephritis is usually of cardiac or iatrogenic origin. Perhaps the most important point in the differential is identification of a nephrotic syndrome somewhere in the patient's past or present. This virtually rules out pyelonephritis as the sole underlying disease.

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Primary Vascular Disease, Including Arteriosclerosis and Essential Hypertension (Nephrosclerosis).—Since both these conditions may produce any degree of renal functional impairment, they bring up the necessity for the most careful distinction between aging of the patient and aging of a disease when it is one which commonly extends over several decades. The pitfalls of such confusion have been emphasized time and again. Some succinct examples are reported by Peters.[32]

The differential largely lies in documenting the natural history of the disease to see whether general vascular degeneration, hypertension, or congestive failure preceded or followed the first identification of renal pathology. In benign nephrosclerosis, proteinuria is usually less than 2 Gm. per day and casts are minimal. In the absence of a history of acute glomerulonephritis or the nephrotic syndrome, without frequent examinations to document the natural history of symptoms and urinary findings, or if the patient is first seen with far-advanced uremia, hypertensive cardiovascular disease, or heart failure, differentiation may be difficult except by renal biopsy. Even with the evidence from the biopsy, the pathologist is sometimes uncertain whether nephrosclerosis preceded or followed glomerulonephritis.

Polycystic Disease.—Polycystic disease is a dominant, nonsex-linked hereditary renal disease which is found in our hospital in 1 of every 165 autopsies, an incidence reflecting the number of patients referred for renal study. Other reported incidences are: Brooklyn, 1 in 158; Boston, 1 in 242; Australia, 1 in 250; Leningrad, 1 in 250; New York, 1 in 428; and Rochester, Minnesota, 1 in 1,019. Hypertension is present in about 60 per cent of the cases and more than 20 per cent have hematuria when first seen by a physician. This disease, similar to glomerulonephritis, has its beginning in childhood and its denouement in the fifth to sixth decade and may sometimes be mistaken for chronic glomerulonephritis. The differential is usually made by family history, presence of abdominal pain, palpable mass or bilateral abdominal masses, x-ray findings, or associated anomalies such as brain aneurysm, or cysts of liver, lung, pancreas, or ureter.

Intercapillary Glomerulosclerosis, or Kimmelstiel-Wilson Syndrome.—Intercapillary glomerulosclerosis, or Kimmelstiel-Wilson syndrome (Fig. 7), can be confused with chronic glomerulonephritis. Proteinuria and hypertension may be present early. When renal infarcts or pyelonephritis are superimposed, hematuria may occur. The nephrotic syndrome with all its laboratory features may supervene and the patient will progress to chronic renal failure and uremia

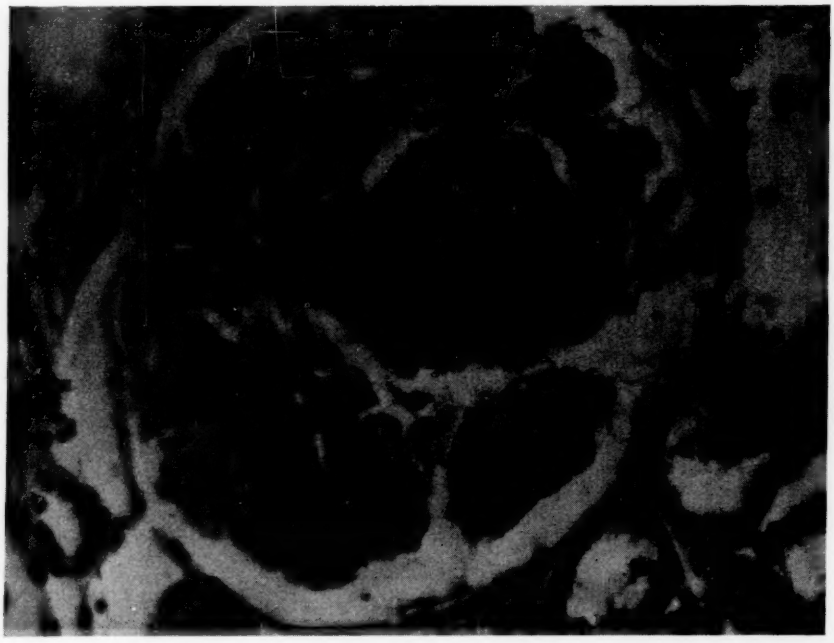

Fig. 7.—The patient is a 58-year-old white woman who was a known diabetic for six years. She was normotensive with no edema. A few microaneurysms were seen in the retina. Proteinuria was 5.3 Gm. per day with many doubly refractile fat bodies. Blood urea nitrogen was 23 mg. per cent, and cholesterol 267 mg. per cent. Thirteen glomeruli appeared in the biopsy, which showed nodular, intercapillary hyaline material, and moderate sclerosis. There is some tubular atrophy, fibrosis, chronic inflammation of stroma, and sclerosis of large arteries. Interpretation: Intercapillary glomerulosclerosis. (Magnification ×270; reduced ¼.)

Diagnosis is usually made by a personal or family history of diabetes mellitus, an abnormal glucose tolerance, capillary microaneurysms in the retina, and the presence of numerous doubly refractile fat bodies in the urine. These may be present even in the absence of the nephrotic syndrome and massive proteinuria. It must be remembered, also, that diabetics can develop glomerulonephritis. Although Fishberg and other authors feel that coexistence of diabetes and glomerulonephritis is rare, we have seen several such instances.

Renal Amyloidosis.—We have studied six patients with nephrotic syndrome due to amyloid in the past three years (Fig. 8). These can occur as "typical" amyloidosis secondary to a suppurative process or as "atypical" amyloidosis. In the latter type, without apparent liver or cardiac involvement, the clinical picture may be indistinguishable from the nephrotic phase of chronic glomerulo-

nephritis. The Congo red test may not be helpful and renal biopsy is the most valuable diagnostic tool. In all of our cases, however, the diagnosis was suspected preceding renal biopsy on the basis of liver, cardiac, or other visceral involvement, or because of a known underlying cause such as osteomyelitis or ulcerative colitis.

Fig. 8.—The patient is a 54-year-old Negro woman with a history of the nephrotic syndrome for one year and anasarca for several weeks. She was normotensive, and had proteinuria of 6 Gm. per day with many doubly refractile fat bodies and glitter cells in the sediment. The blood urea nitrogen varied from 10 to 30 mg. per cent. Cholesterol was 470 mg. per cent. Twelve glomeruli appeared on the renal biopsy, which showed amyloid deposits in the walls of the capillaries and small blood vessels. Many tubules show focal atrophy and hyaline and giant cell casts. Congo red stain was positive. Interpretation: Amyloid nephrosis. (Magnification ×440; reduced ¼.)

Renal Lesions of Systemic Lupus Erythematosus.—The renal lesions of systemic lupus erythematosus are being identified with increasing frequency. The clinical and even the pathologic findings may be almost indistinguishable from those of diffuse glomerulonephritis. The term "lupus sine lupo" has been used to designate patients with visceral lesions of systemic lupus who lack the classical rash. We have encountered several patients with few visceral manifestations except for a presenting renal disease which may be predominantly nephritic, predominantly nephrotic, or mixed. Without a positive LE preparation, the diagnosis of lupus may be elusive on clinical grounds. The following case illustrates how a fulminating case of renal lupus may imitate glomerulonephritis in its successive phases of hemorrhagic nephritis, nephrotic syndrome, and death in uremia.

Case 3.—A 23-year-old girl was admitted with ankle, facial, and periorbital edema. She was in good health until the age of 21, when proteinuria was noted on one urinalysis following

a tooth extraction. Two months prior to admission a routine urinalysis revealed proteinuria and hematuria. One month later she had periorbital and ankle edema and a sore throat. Four days prior to admission she noted flank pain, fever, and increased edema. On examination she was normotensive and afebrile and had pretibial, retinal, and marked periorbital edema. A working diagnosis of acute glomerulonephritis was made. She developed proteinuria of 7.6 Gm. per 24 hours. Addis counts revealed 3 million red cells, 1.5 million white and epithelial cells, and 2.3 million casts per 24 hours. Fresh urine showed red cells and hyaline casts with renal epithelial cells and many doubly refractile fat bodies. The serum urea nitrogen was 22, creatinine 1.3, and cholesterol 330 mg. per cent. Total serum proteins were 4.7 Gm. per cent with an albumin-globulin ratio of 2.5/2.2. She had anemia (hematocrit 34) and luekopenia (4,200 white cells). Throat and urine cultures, blood Wassermann, and search for lupus cells were negative. The antistreptolysin titer was not increased. The creatinine clearance was 90 ml. per minute and the phenolsulfonphthalein excretion was 30 per cent in fifteen minutes.

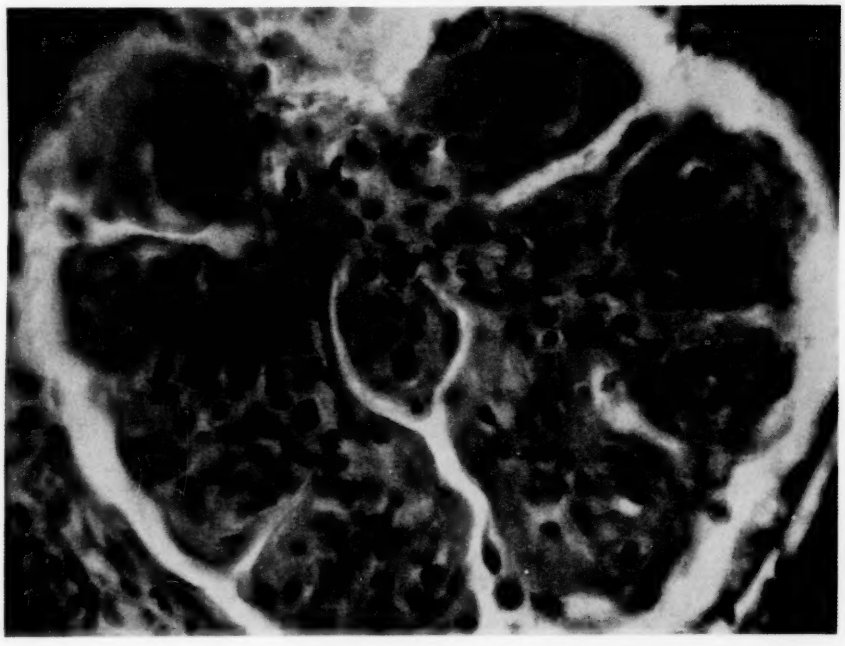

Fig. 9.—Patient 3. Glomeruli show digitation with focal, homogeneous thickening in several segments which show verrucal capillaritis, fibrinoid degeneration, and typical "wire-loop" formation. The lesion was unusually diffuse and necrotizing. Interpretation: Systemic lupus erythematosus. (Magnification ×400; reduced ¼.)

Course.—On bed rest she had a 9-pound diuresis and improved clinically. Three weeks later she developed acute neck pain diagnosed as thyroiditis, but thyroid function tests were normal. Following this she developed progressive nausea, vomiting, edema, ascites, and anasarca. White cells and desquamated renal epithelial cells within hyaline casts increased in number. The blood urea nitrogen rose to 102 mg. per cent. A trial of ACTH (40 units twice a day) produced no change in quantitative protein excretion or the clinical course. After it, however, 12 typical lupus cells were found in a single preparation. No diuresis occurred following withdrawal of ACTH or during subsequent treatment with hydrocortisone. The course was rapidly downhill with minor periods of clinical improvement. She developed nausea, vomiting, headache, hypertension, blurring of vision, extensor muscle twitches, encephalopathy, Jacksonian convulsions, psychosis, muscle wasting, lethargy, and coma. The serum cholesterol rose to 434 mg. per cent and pro-

teinuria increased to 10 Gm. per 24 hours. The total serum protein decreased to 3.0 Gm. per cent with an albumin-globulin ratio of 1.9/1.1. Broad renal failure casts appeared together with red cell, granular, epithelial cell, and fatty casts—a true telescoped urine. Steroids were discontinued, following which the patient showed considerable clinical improvement. She was discharged on the eighty-ninth hospital day. Seven weeks later she was readmitted with dehydration, acidosis, congestive failure, pulmonary edema, severe anemia, and azotemia. She died five months after the onset of her disease. Classical lesions of renal lupus erythematosus were found at autopsy (Fig. 9).

In lupus, the inflammatory lesion in the glomerulus is usually a focal homogeneous thickening of one or more glomerular segments with wire loop formation or verrucal capillaritis progressing to fibrinoid thickening, degeneration, and hyalinization. The capillary changes are more eosinophilic than in acute glomerulonephritis. Clinically, the most distinguishing features of disseminated visceral lupus are positive LE cells in bone marrow or blood, telescoped urinary sediment,[9,10] predilection for females, photosensitivity, fever, arthralgia, butterfly rash, pleuritic and peritoneal pain, cerebral manifestations, anemia, leukopenia, thrombocytopenia, hyperglobulinemia, and a tendency to have many white cell inclusions in the hyaline casts. Despite statements in the older literature to the contrary, in our experience hypertension, retinopathy, and even encephalopathy are not uncommon with this disease.

Progressive Systemic Sclerosis (Scleroderma).—Progressive systemic sclerosis (scleroderma) is characterized by primary involvement of interlobular arteries with intimal and medial thickening and fibrinoid necrosis. These patients may have a fulminating hypertension and uremia even in the absence of extensive skin lesions. Hematuria is not uncommon, especially with a malignant hypertension.[33] We have encountered doubly refractile fat bodies and a telescoped urinary sediment in this disease. The diagnosis is usually apparent from the skin, esophageal, or other visceral manifestations of scleroderma. Renal biopsy is important in the atypical cases.

Nephrocalcinosis.—Any of the diseases associated with nephrocalcinosis may present with renal failure, hypertension, and hematuria and resemble chronic glomerulonephritis. This has been true in our experience with renal hyperchloremic acidosis[34,35] and may also be seen in the milk-alkali syndrome,[36,37] hyperparathyroidism, vitamin D intoxication,[38] and sarcoidosis.[39] A history of the underlying situation (e.g., milk and alkali for a peptic ulcer, vitamin D for arthritis), hematuria, recurrent pyelonephritis, the passage of stone or gravel, and the characteristic x-ray findings of nephrocalcinosis will aid in the diagnosis. Renal biopsy may identify nephrocalcinosis deep in the medulla before it is radiographically discernible.

Uric Acid Nephritis.—Uric acid nephritis may be seen in patients with gout, leukemia, lymphoma, and especially following uricosuric drugs, radiation, triethylene melamine, nitrogen mustard, and other cytotoxic agents which are being used with increasing frequency in the therapy of neoplasm. In the acute phase, ureteral colic, acid urine, and uric acid crystals accompany the hematuria and proteinuria. In the elderly patient, uric acid nephritis usually coexists with nephrosclerosis or pyelonephritis and may resemble chronic glomerulonephritis. A history of gout or administration of uricosuric agents, elevated

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blood uric acid (disproportionate to azotemia), renal tenderness, identification of uric acid stones, the presence of urate crystals in casts or persistent crystalluria and acid urine are helpful in making the differential diagnosis.

DISCUSSION

The differential diagnosis of acute and chronic glomerulonephritis requires meticulous attention to personal and family medical history, thorough physical examinations, and skillful direction of the patient through a variety of blood, urine, x-ray, and renal function tests.

More importantly it requires a difficult reorientation of the physician toward a study of the natural history of prolonged disease, a concept seldom gleaned from modern house staff training with its rapid rotations from service to service and the necessarily episodic exposure to only those complications of glomerulonephritis demanding hospitalization.

The modern well-trained clinician can make correct etiologic diagnoses of the majority of renal diseases with greater accuracy and frequency than was possible a few years ago. This has prevented many patients from being classified under the defeatist terms of "terminal uremia," "chronic Bright's disease," or "renal failure" and has made possible new approaches to effective therapy. Clinical investigators in the field of renal diseases have achieved a surprising synthesis of bedside medicine and modern laboratory techniques. The organization of renal clinics, kidney research laboratories, and specialized scientific societies has bettered medical education in this long-neglected field. Advances have come from re-emphasis on, and improved methods in examination of, the urinary sediment, plus the development of new serologic and bacteriologic techniques. Renal biopsy has stimulated a renewed interest in the study of renal pathology and the correlation between the clinical picture and functional and histopathologic findings.

Debate will continue on whether we have come a long or a short way since Richard Bright. Few will deny that we have a long way to go. Accurate etiologic diagnosis has been and will continue to be a sine qua non for clinical progress in glomerulonephritis.

SUMMARY

The differential diagnosis of acute and chronic glomerulonephritis includes a wide variety of organic renal and vascular diseases together with some of the functional causes of proteinuria.

The modern clinician can improve his diagnostic accuracy and therapy by proper integration with the laboratory. The most important advances in this field have come from improved examination of the urinary sediment, better bacteriologic studies, more widespread use of serologic techniques such as the antistreptolysin titer and measurement of serum complement, more frequent testing of discrete renal functions, and the recent introduction of renal biopsy, which permits invaluable correlation between clinical findings, function, and histology.

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These laboratory aids supplement but will never supplant keen observation and the continued delineation of the natural history of glomerulonephritis.

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THE SIGNIFICANCE AND POTENTIAL VALUE OF RENAL BIOPSY IN BRIGHT'S DISEASE

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IN 1939, Iversen and Roholm[1] introduced a safe technique for percutaneous needle biopsy of the liver. This was followed by its widespread use in the diagnosis, management, and investigation of diseases affecting that organ. Today, seventeen years later, the results achieved by hepatic biopsy are apparent to all. The clinical and histologic pictures of the most important diseases of this organ have been delineated and the natural histories of a number of diseases, such as viral hepatitis, have been described. The potentialities of the new technique of serial percutaneous biopsy of the kidney are certainly no less than for the liver and are only now beginning to unfold.

Today the terms *Bright's disease* and *glomerulonephritis* are still used in a wide sense because we cannot clearly distinguish on clinical grounds the varying pathologies which affect the kidneys of our patients. This is especially true when patients suffer from the nephrotic syndrome. Unless it can be established that the patient has diabetes mellitus or generalized amyloidosis, the physician has been driven to conclude that the patient is suffering from glomerulonephritis—a scrapbasket which contains cases of "lipoid nephrosis," systemic lupus erythematosus, amyloidosis, and renal vein thrombosis, among the many causes of the nephrotic syndrome. Moreover, in cases of chronic renal failure with contraction of the kidneys ("end stage kidney"), it has often been impossible to make an exact diagnosis from the clinical data—and at times, even in the post-mortem room.

As we shall show, renal biopsy allows one to distinguish and classify more exactly the manifold conditions which affect the kidney and which have been

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called, collectively, Bright's disease; it is most valuable in the assessment of prognosis and in the management of certain patients with glomerulonephritis; it has our improved understanding of the natural history of kidney disease and it harvests living tissue for many basic studies (chemical, histologic, electron-microscopic, histochemical, and bacteriologic), some of which have already laid sound foundations for the improved care of patients.

SOME REMARKS ON RENAL BIOPSY STUDIES IN BRIGHT'S DISEASE

In this communication, patients with Bright's disease will be discussed from the point of view of their presenting *clinical* picture. They fall into three groups: acute hemorrhagic Bright's disease; edematous (so-called "subacute") Bright's disease; and chronic (nonedematous) glomerulonephritis, or Bright's disease.[2] Unhappily, these clinical connotations are not necessarily identical with the pathologist's classification of acute, subacute, or chronic glomerulonephritis.

Acute Hemorrhagic Bright's Disease.—Iversen and his colleagues[3] have reported biopsy studies on 6 patients with acute hemorrhagic glomerulonephritis. Slight proliferation of epithelial and endothelial cells of the glomerular tuft and slight diffuse hyalinization of the basement membrane were noted. The convoluted tubules were normal, but blood was found within the lumina of the distal tubules. Howe[4] found similar changes in the glomeruli but also noted degenerative changes in the tubules. In one of Iversen's patients there were, in addition, some partially hyalinized glomeruli, synechiae, and a single epithelial crescent. This patient had probably had a previous attack of glomerulonephritis. Iversen and his associates expressed surprise at the scantiness of the glomerular changes which may, perhaps, be accounted for by the fact that the pathology in their cases was less severe than is usual in patients dying of acute glomerulonephritis. The histologic changes observed by these authors and by ourselves are similar to those reported from autopsy studies, except that, in no case to date, have erythrocytes been seen in Bowman's space, although they do appear in the tubules.

The following case is presented to illustrate changes observed in serial biopsies:

A. O'N., a 20-year-old apprentice cabinetmaker, was admitted to the hospital on May 7, 1955. He had been in good health until one week before admission, when he developed swelling of the ankles and puffiness around the eyes. The following day he noticed that his urine was bloody and that the quantity passed had diminished. On examination, he had slight generalized edema and a blood pressure of 155/90 mm. Hg. The urine contained 4+ protein, very many erythrocytes, and hyaline and erythrocyte casts. A clinical diagnosis of acute hemorrhagic glomerulonephritis was made. He was kept at rest in bed for six weeks and then gradually resumed activity. His urine still contained 1 to 3 Gm. of protein per 24 hours and erythrocytes and erythrocyte casts. Eleven months after the onset of his illness, protein is still found in his urine, but other tests of renal function are normal. Red cells and erythrocyte casts disappeared from the urine in January, 1956. Three renal biopsies were made—in May, 1955; in September, 1955; and in April, 1956.

The First Renal Biopsy (*Fig. 1*).—This was performed on May 13, 1955. The glomeruli were somewhat lobulated and were markedly hypercellular. The hypercellularity was due both to endothelial cell proliferation and to exudation of polymorphonuclear leukocytes within the

glomerular tufts. The basement membrane was slightly thickened. The capillary lumina were somewhat narrowed and contained a few erythrocytes. Bowman's spaces contained no protein. A few small adhesions between the tuft and Bowman's capsule were noted. There were marked degenerative changes of the epithelium of the convoluted tubules, which were somewhat dilated and contained a moderate amount of proteinaceous material. There was distinct edema but no inflammation of the interstitial tissue. The small arteries and arterioles were normal.

Diagnosis: The histologic picture was consistent with the diagnosis of *acute glomerulonephritis.* The presence of a few glomerular adhesions indicated either that the acute process had gone on for longer than the history would indicate or that there might have been a previous attack of glomerulonephritis—of which there was no history. An alternative and more likely explanation is that the velocity of the process was such that it produced adhesions within two weeks.

Second Renal Biopsy (*Fig. 2*).—This was performed on Sept. 9, 1955. There was hypercellularity of some of the glomeruli. A few neutrophils were again seen in the glomerular tufts. Some glomeruli were congested and others were bloodless (these were more severely damaged). In a few glomeruli, well-developed fibrous adhesions between the tuft and Bowman's capsule were seen; in others there were fibroepithelial crescents. Bowman's spaces contained abundant proteinaceous material. There were moderate to severe degenerative changes of the epithelium of the convoluted tubules which contained abundant proteinaceous material. There was mild fibrosis and edema of the interstitial tissue which was infiltrated by small scattered foci of chronic inflammatory cells. The small arteries and arterioles were normal.

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Diagnosis: This histologic picture was consistent with the pathologic diagnosis of *subacute glomerulonephritis.* In some glomeruli there was evidence of progression with fibroepithelial crescent formation, and in others the endothelial cell proliferation and neutrophil infiltration indicated that the process was still acute. The clinical diagnosis at this time was persistent acute hemorrhagic Bright's disease with no evidence of the nephrotic syndrome.

Third Renal Biopsy (*Fig. 3*).—This was performed on April 20, 1956. There was minimal local thickening of the basement membrane in most of the glomeruli. In one or two glomeruli there were small areas of mild hypercellularity. In other respects the glomeruli were entirely normal; their capillary lumina were moderately dilated and contained many erythrocytes. Adhesions and epithelial crescents were not seen. There was no proteinaceous material in Bowman's spaces. Moderate degenerative changes were seen in the lining epithelium of the convoluted tubules; their lumina contained a small amount of proteinaceous material. The interstitial tissue was normal, as were the small arteries and arterioles.

Diagnosis: At first this histologic picture appeared to be within normal limits. However, *a very mild membranous glomerulonephritis* was noted on closer study. The hypercellularity and exudative changes seen in the first two biopsies have disappeared. This indicates a marked improvement in the histologic picture; the disappearance of erythrocytes and erythrocyte casts from the urine indicates a similar improvement in the patient's health. Proteinuria 1 to 2 Gm. per 24 hours still persists.

Subacute Edematous Glomerulonephritis (*Nephrotic Syndrome*).—In patients whose sole presenting symptom is the gradual or more rapid onset of edema, the difficulties of exact clinical diagnosis are well known. It is in this group of patients that renal biopsy has played a particularly significant role in establishing an exact diagnosis. Alwall[5] first demonstrated this in 1944 when he diagnosed renal amyloidosis from the biopsy done on a woman ill with the nephrotic syndrome. It is noteworthy that of the first 8 patients with the nephrotic syndrome studied by Iversen and his co-workers, 4 were found to have renal amyloidosis.[3] In addition to the various forms of Bright's disease, we have found the nephrotic syndrome in association with systemic lupus erythematosus,[6] primary renal amyloidosis,[7] renal vein trombosis,[8] diffuse diabetic

Fig. 1.

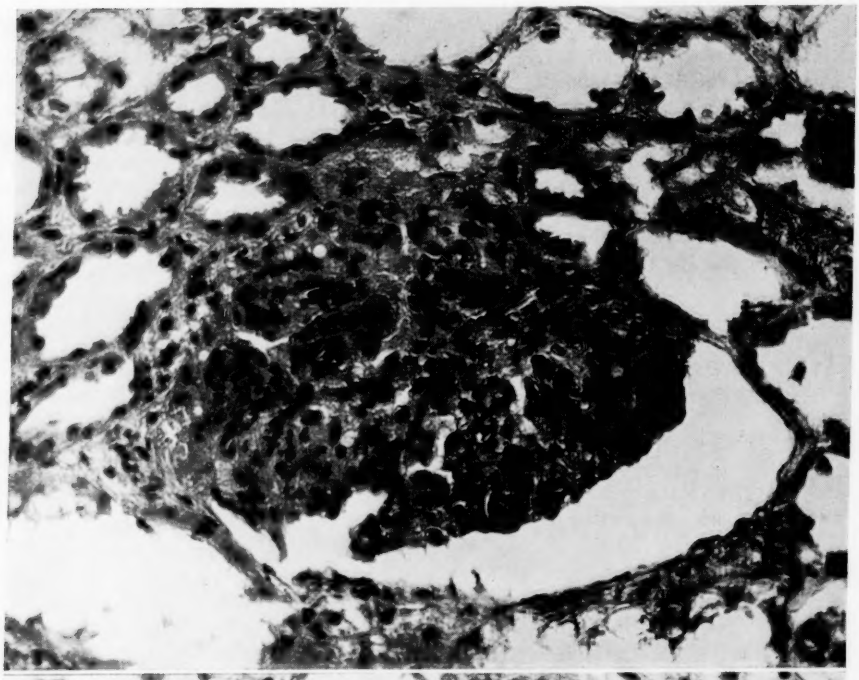

Fig. 2.

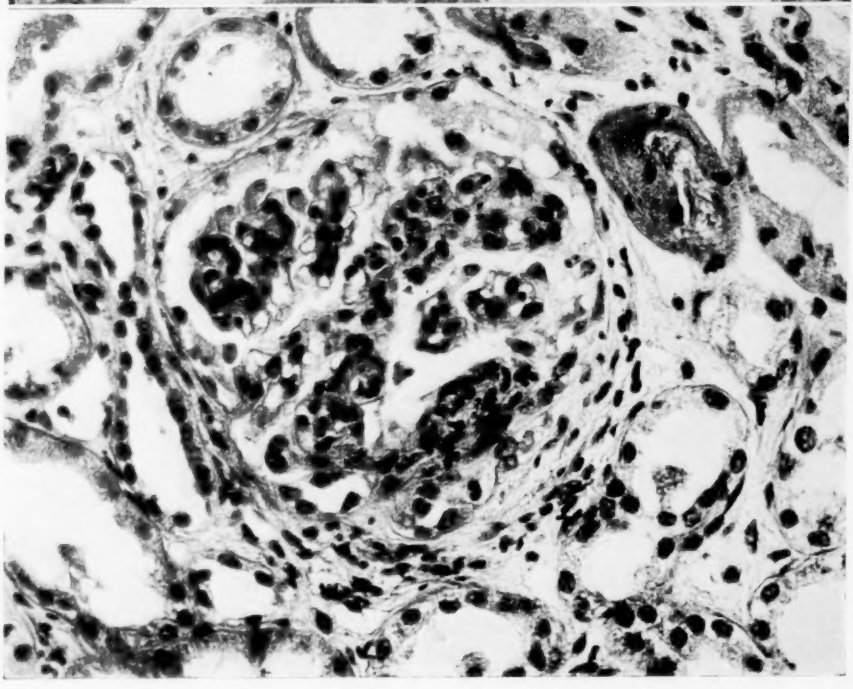

Fig. 1.—First biopsy made two weeks after onset of symptoms. Note the marked cellular proliferation in the glomerular tuft. The capillary lumina are narrowed and contain few erythrocytes. (Hematoxylin and eosin × 410; reduced ⅙.)

Fig. 2.—Second biopsy made five months later. There is still considerable cellular proliferation. Note the fibroepithelial crescent. (Hematoxylin and eosin × 440; reduced ⅙.)

glomerulosclerosis,[9] and following treatment of hypertensive patients with mercurial diuretics and antihypertensive agents.[10]

Ellis[11] described two types of Bright's disease in association with the nephrotic syndrome; he found definite differences in the clinical and pathologic features in the two groups of patients. Enticknap and Joiner[12] repeated Ellis's work, and pointed out that Ellis types I and II nephritis were not mutually exclusive entities. Davson and Platt[13] were able to distinguish these two types of Bright's disease in the majority of their cases but could not decide whether types I and II nephritis were variations of the same disease. In a recent clinical study, Clark[14] concluded that nephritis could not be divided into two clear-cut types, as Ellis had suggested. We have noted lesions of both types of nephritis—separately and together—in sections of renal tissue removed by biopsy. In

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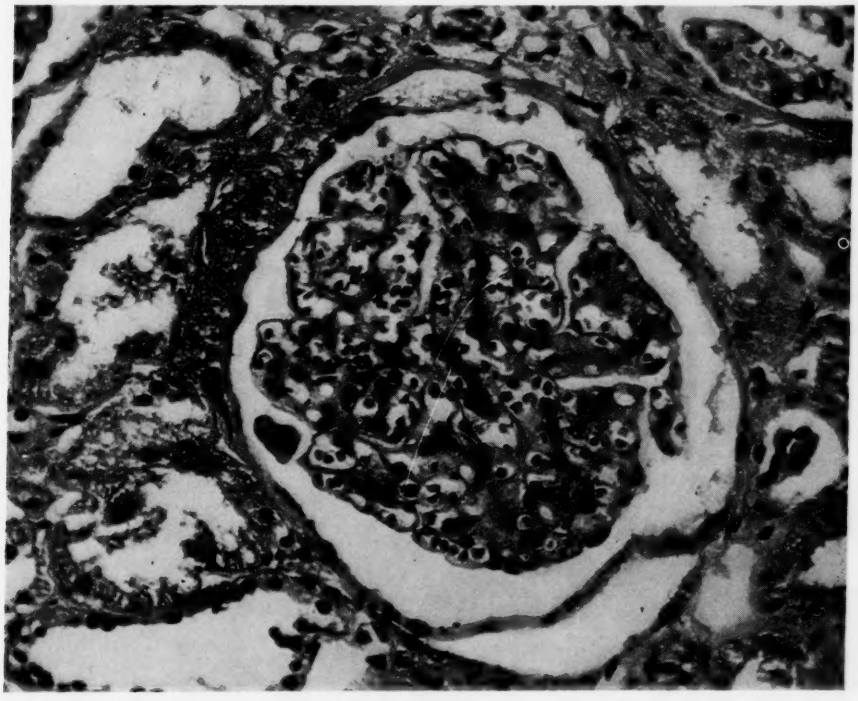

Fig. 3.—Third biopsy made eleven months after the onset of symptoms. Note that the glomerulus is normal. In other glomeruli a few small areas of slight hypercellularity were seen. (Hematoxylin and eosin × 410; reduced 1/6.)

addition, a new and unique histologic picture has been observed in sections of kidney from adult patients with the nephrotic syndrome.[15] The degenerative tubular changes and congested glomeruli observed will be described later.

Membranous and Proliferative Glomerulonephritis.—Of the 56 adult patients with the nephrotic syndrome studied, few gave a history of acute hemorrhagic Bright's disease, and only an occasional patient was ***known*** to have had proteinuria for some time prior to the appearance of edema. In these 56 patients,

Fig 4.

Fig 5.

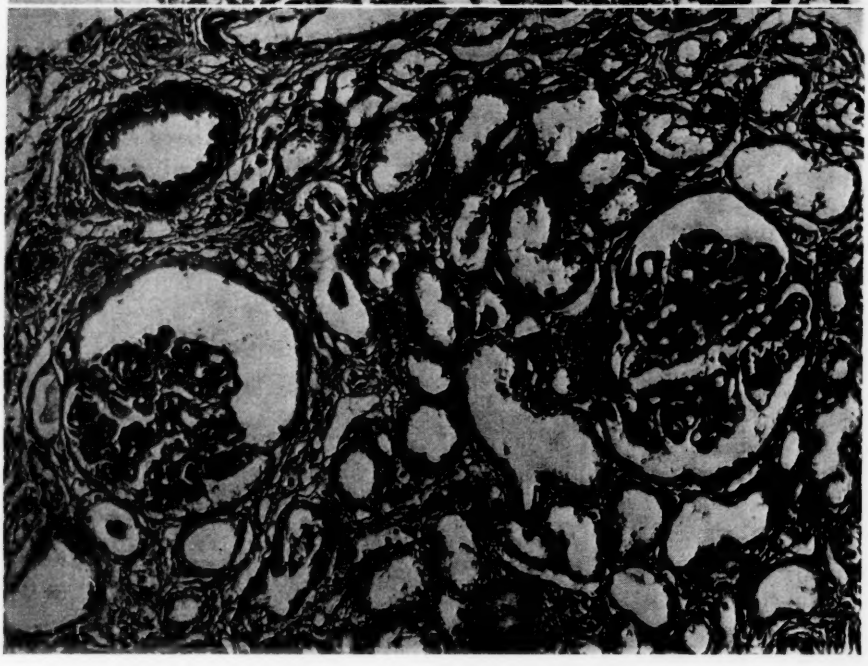

Fig. 4.—Biopsy taken from a 29-year-old Negro female six months after the onset of the nephrotic symdrome. The blood pressure was normal, there was no azotemia, and renal function was slightly depressed. Note the moderate diffuse thickening of the basement membrane in this representative glomerulus. There is a moderate degree of tubular degeneration. Diagnosis: Membranous glomerulonephritis. (Hematoxylin and eosin × 410; reduced ⅙.)

Fig. 5.—Biopsy taken from a 47-year-old white man six months after the onset of the nephrotic syndrome. The blood pressure was normal, there was minimal azotemia, and renal function was slightly depressed. Note the marked generalized thickening of the glomerular basement membrane, the tubular damage, and the interstitial edema and fibrosis. Diagnosis: Membranous glomerulonephritis—more severe than in the previous case. (Hematoxylin and eosin × 225; reduced ⅙.)

who were cast in the same clinical mold, the histologic picture varied considerably. Laboratory data have not been of value in forecasting the underlying pathology.[9] We have observed the classical pathologic appearances of proliferative and membranous glomerulonephritis (Ellis types I and II, respectively) in the majority of our patients with the nephrotic syndrome; certain findings, however, deserve emphasis. In several cases we have been impressed with the fact that, even early in the disease, soon after the onset of edema, glomerular changes of many kinds and of varying severity may be found (Figs. 4 to 6). In some instances glomeruli with proliferative changes (Ellis type I) and others with hyaline basement membrane changes (Ellis type II) were seen in the same sections; in some cases, features of both types of change were seen in the same glomeruli. Reubi[16] stated that by renal biopsy he could distinguish cases with membranous from those with proliferative glomerular changes. In our experience this certainly has not been true in all cases.

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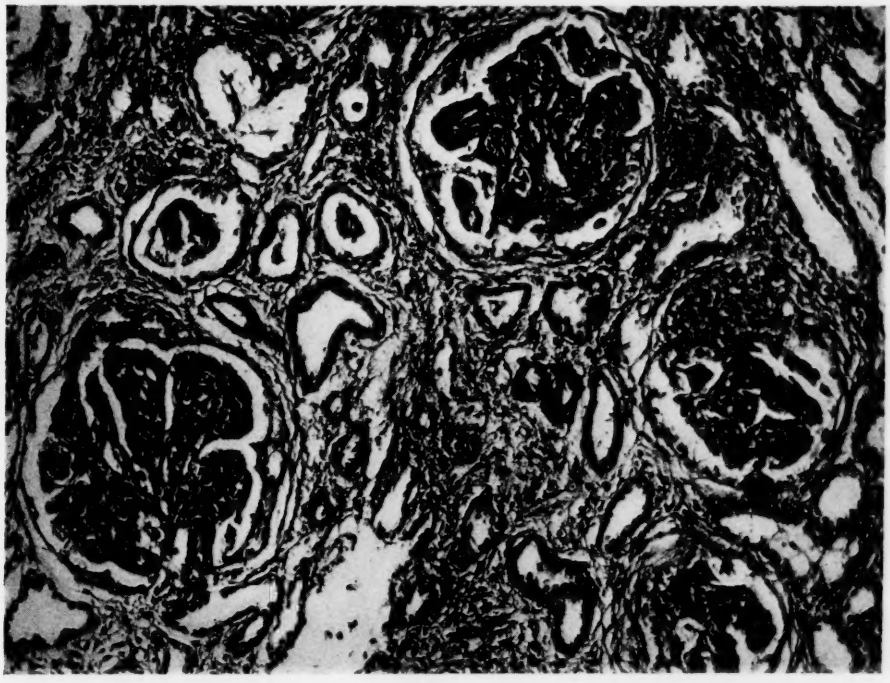

Fig. 6.—Biopsy taken from a 14-year-old schoolboy two months after the onset of the nephrotic syndrome and three months after a brief episode of hematuria. The blood pressure was normal, there was moderate azotemia, and renal function was depressed. Note the severe diffuse thickening of the glomerular basement membrane and the mild hypercellularity of the tufts, some of which are lobulated. A typical fibroepithelial crescent is seen. Note the marked interstitial fibrosis and tubular atrophy. Diagnosis: Advanced membranous and proliferative glomerulonephritis. (Hematoxylin and eosin × 200; reduced ⅙.)

Edema of the interstitial tissue of the kidney has been a prominent histologic feature early in the nephrotic syndrome, and superimposed chronic pyelonephritis and/or interstitial nephritis has appeared later in the disease. The other findings, such as tubular degeneration, do not differ essentially from those described in the classical textbooks of pathology.

Nephrotic Syndrome With Predominant Tubular Degeneration ("Lipoid Nephrosis").—The existence of the entity "lipoid nephrosis" has been a source of controversy for many years. Most cases have been thought to occur in children and few have been described in adults. By means of renal biopsy, Bjørneboe and his co-workers[17] found lipoid nephrosis in one patient with the nephrotic syndrome and Joske[18] diagnosed lipoid nephrosis in one of his patients. Allen,[19] and others, in their studies of autopsy material, are of the opinion that the glomerular basement membrane is thickened in the kidneys of all patients having the nephrotic syndrome. Yet, neither Joske nor Bjørneboe reported basement membrane changes in their patients, save for slight hyaline thickening in 3 of the 22 glomeruli in Bjørneboe's patient.

Fig. 7.—Biopsy taken from an 82-year-old man one month after the onset of the nephrotic syndrome. The blood pressure was normal, there was minimal azotemia, and renal function was slightly depressed. Except for a marked increase in the number of erythrocytes in the capillary loops, the glomeruli are essentially normal. Note the moderate tubular degeneration. Diagnosis: Nephrotic syndrome with predominant tubular degeneration. (Hematoxylin and eosin × 300; reduced ⅓.)

In 6 of our patients with the nephrotic syndrome, no organic structural damage was observed in the glomeruli. Their ages ranged from 15 to 82 years. They presented with a history of gradual onset of edema, and edema was the only positive physical finding. All had massive proteinuria, hypoalbuminemia, and hypercholesterolemia. Casts and doubly refractile bodies were found in their urine. Study of the renal biopsies revealed neither proliferative changes nor thickening of the glomerular basement membrane, which was thin and delicate. In these biopsies there was an increased number of red cells in the glomerular tuft in contrast to the normal glomerulus, which contains but few

erythrocytes in biopsy material. The most striking abnormality was severe tubular degeneration with considerable fat deposition in the tubular epithelium. The tubular epithelium was comparatively low, and the capsular spaces and tubular lumina contained abundant proteinaceous material. There was well-marked edema of the interstitial tissue (Fig. 7). With regard to this singular renal histologic picture, one similar case of nephrotic syndrome in a 20-year-old man was reported by Payet and his colleagues[20]; they found very marked tubular changes and congested glomeruli.

When treated with ACTH, these patients had excellent diuresis. A second biopsy was made in 2 patients at the height of diuresis. The previously congested glomeruli now contained a normal number of erythrocytes, and their basement membranes (as in the first biopsies) were normal. There was much less degenerative change in the tubules, and the interstitial edema was no longer seen.[9]

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In one of these patients, a 65-year-old arteriosclerotic grandmother, slight thickening of the glomerular basement membrane developed eighteen months after she was first studied. When last studied, the others were histologically normal. One 15-year-old school boy has been followed for sixteen months and is at present clinically and histologically normal. Three other patients who had had a nephrotic syndrome were studied for the first time only after they had lost their edema by diuresis and were clinically normal. No abnormality was found in the kidney biopsies.

Chronic Nonedematous Glomerulonephritis.—Clinically, chronic Bright's disease may represent the terminal stage of a variety of diseases and a variety of clinical courses for any one disease. Some of the patients to be described gave a history of acute hemorrhagic Bright's disease, others had had the nephrotic syndrome, some were known to have had protein and casts in their urine for long periods of time, and others had been unaware of any symptoms or signs of Bright's disease in the past. In our experience, unless there was a clear history of acute hemorrhagic glomerulonephritis or of the nephrotic syndrome, exact clinical diagnosis in patients with azotemia and decreased renal reserve was rarely possible. The distinction from chronic pyelonephritis was found to be especially difficult. Reubi[21] described the first case in which renal biopsy clearly differentiated between chronic glomerulonephritis and chronic pyelonephritis; and we have seen one patient in whom clinically unsuspected acute pyelonephritis and many in whom unsuspected chronic pyelonephritis were superimposed on instances of chronic glomerulonephritis.

It is well known that when some patients with chronic kidney disease die, the morphologic changes in the kidney may be such that exact pathologic diagnosis is either difficult or impossible. If such patients are studied by renal biopsy at an earlier stage, the pathologic diagnosis may be easier. In general the pathologic findings in renal biopsies of patients with chronic glomerulonephritis do not differ qualitatively from those seen in autopsy material. However, we have been impressed by the frequency of inflammatory changes in the interstitial tissue with evidence of superimposed pyelonephritis or interstitial nephritis. The importance of interstitial renal infection in chronic glomerulo-

nephritis has not been stressed in the past and will be reported in detail at a later date. To date, cultures made from the renal tissue have grown out organisms in a few cases, *Staphylococcus aureus* and hemolytic enterococci being most frequently encountered. Sclerosis of small arteries, arterioles, and afferent arterioles was found in many instances.

THE STUDY OF THE NATURAL HISTORY OF BRIGHT'S DISEASE

It was John Ryle[22 23] who drew attention to the importance of the study of the natural history of disease and to the importance of this knowledge in the evaluation of methods of treatment. The rapid therapeutic advances of the present era can be accurately evaluated only in the light of a good understanding of the natural history of disease. This is especially true with those diseases which produce glomerulonephritis—diseases in which the clinical course is so variable.

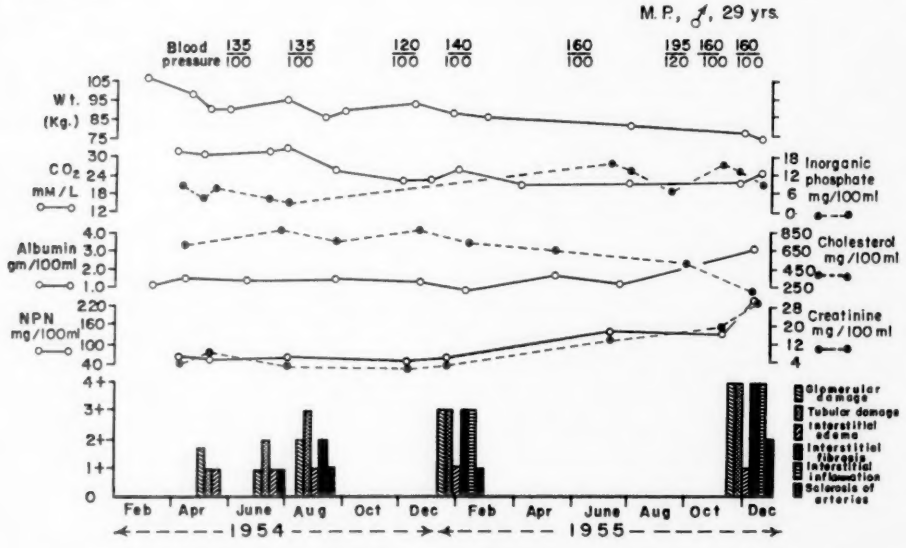
M.P., ♂, 29 yrs.
Blood pressure 135/100 135/100 120/100 140/100 160/100 195/120 160/100 160/100
Wt. (Kg.) 105 95 85 75
CO_2 mM/L 30 24 18 12
Inorganic phosphate mg/100ml 18 12 6 0
Albumin gm/100ml 4.0 3.0 2.0 1.0
Cholesterol mg/100ml 850 650 450 250
NPN mg/100ml 220 160 100 40
Creatinine mg/100 ml 28 20 12 4
4+ 3+ 2+ 1+ 0
Glomerular damage
Tubular damage
Interstitial edema
Interstitial fibrosis
Interstitial inflammation
Sclerosis of arteries
Feb Apr June Aug Oct Dec Feb Apr June Aug Oct Dec
1954
1955

Fig. 8.—Patient M.P. Chart illustrating some features of the natural history of a case of subacute edematous glomerulonephritis. Note the steady deterioration in the biochemical findings. However, between November, 1954, and April, 1955, there was a period of more rapid deterioration with a marked rise in the levels of blood creatinine and NPN, a marked rise in the serum inorganic phosphate, and a significant fall in the CO_2 combining power. Histologically, note the appearance at this time of marked interstitial inflammation and the increase of interstitial fibrosis.

It is premature at this time to report detailed observations on the natural history of Bright's disease. Thus, a concise example must suffice to show the potential value of the method of study we are using.

M. P., a 29-year-old Negro kitchen hand was in good health until February, 1954. At this time, ten days after a "head cold," his legs began to swell; and when first seen in April, 1954, he had anasarca, massive proteinuria, cylindruria, hypercholesterolemia, and hypoalbuminemia. A clinical diagnosis of subacute edematous glomerulonephritis was made. Subacute proliferative glomerulonephritis was found on study of the renal biopsy (Table I and Fig. 9). Despite the administration of hormones, diuretic agents, and a low salt diet, he had no satisfactory sustained

diuresis. He lost some edema fluid in August, 1954, after a course of intravenous salt-poor human albumin, but edema rapidly reaccumulated. From January to July, 1955, there was a gradual deterioration of his condition with increasing azotemia. The findings of the nephrotic syndrome persisted throughout. Despite close dietary supervision, his condition deteriorated rapidly thereafter and he died in December, 1955, in severe chronic uremia. The progression of the histologic changes is set forth in Table I and Figs. 9 to 12, and some of the biochemical changes are shown in Fig. 8.

At the post-mortem examination, generalized edema, bilateral hydrothorax, and ascites were found. The heart was moderately hypertrophied and weighed 540 Gm.; there was a uremic pericarditis. Passive congestion was found in all the viscera; it was most marked in the liver.

TABLE I. DETAILED ANALYSIS OF RENAL HISTOLOGY OF FOUR SERIAL BIOPSY SPECIMENS AND AN AUTOPSY SPECIMEN FROM PATIENT M.P., ILL WITH THE NEPHROTIC SYNDROME*

ANALYSIS OF RENAL HISTOLOGY	BIOPSY I MAY 8/54	BIOPSY II JULY 13/54	BIOPSY III AUG. 24/54	BIOPSY IV JAN. 31/55	AUTOPSY DEC. 27/55
Glomeruli:					
Cellularity	++	+	+	+	+
Basement membrane thickening	+	+	++	+++	++++
Ischemia	+	0	++	+++	+++
Lobulation	+	0	+	0	+
Adhesions or crescents	+	0	+	+++	+++
Hyalinization of glomeruli	0	0	0	+++	+++
Thickening of Bowman's capsule	0	0	0	+	+++
Protein in Bowman's space	+	+	0	0	+
Glomerular Damage	++	+	++	+++	++++
Tubules:					
Degeneration	+	+++	+++	+++	+++
Atrophy	0	+	+	++	++++
Dilatation	+	++	++	0	++++
Tubular lumina:					
Protein	+	++	++	++	++++
Casts	0	0	0	++	+++
Polymorphonuclear leukocytes	0	0	0	++	++
Tubular Damage	+	++	+++	+++	++++
Interstitial tissue:					
Edema	+	+	+	+	+
Fibrosis	0	+	++	+++	++++
Inflammation	0	0	0	+++	++++
Arteries:					
Sclerosis	0	0	+	+	++

***Note:* (a) May 18, 1954. The biopsy confirmed the clinical diagnosis of subacute edematous Bright's disease. Hypercellularity of the glomerulus was a prominent finding (Fig. 9).**

(b) July 13, 1954. The glomerular hypercellularity is less prominent, and the degeneration of the tubular epithelium is marked (Fig. 10).

(c) Aug. 24, 1954. Basement membrane thickening is now more prominent. Interstitial fibrosis has become prominent and sclerosis of the vessels is evident. A pathologic diagnosis of chronic glomerulonephritis was made.

(d) Jan. 31, 1955. There is now thickening of Bowman's capsules, increasing tubular atrophy, casts, and polymorphonuclear leukocytes in the tubular lumina, and marked inflammatory changes in the interstitial tissue, indicating a superimposed pyelonephritis (Fig. 11). This was not diagnosed clinically.

(e) Dec. 27, 1955. Autopsy findings of chronic glomerulonephritis and superimposed pyelonephritis in both kidneys confirmed the previous biopsy findings (Fig. 12).

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The kidneys weighed 130 and 160 Gm. Their capsules stripped with ease, exposing fine, granular, pale, red-brown surfaces. On section, the cortex was reduced in thickness, and in the medulla there were prominent linear yellowish markings radiating toward the papillae. The renal pelves, ureters, and urinary bladder were normal.

THE CLINICAL VALUE OF RENAL BIOPSY IN THE DIAGNOSIS, PROGNOSIS, AND MANAGEMENT OF GLOMERULONEPHRITIS

Management and prognosis of Bright's disease will be put on a more rational basis when the various forms of glomerulonephritis can be clearly delineated and recognized. In this regard, by means of renal biopsy studies, we have separated from the general group of Bright's disease a specific form of glomerulonephritis—lupus nephritis.[6,24] The lesions of this disease can now be recognized in the kidney, even in the absence of the skin lesions of systemic lupus erythematosus.

Acute Hemorrhagic Bright's Disease.—In most children in whom gross hematuria and proteinuria occur soon after hemolytic streptococcal infection of the upper respiratory tract, the clinical diagnosis of acute glomerulonephritis is straightforward. In adults, Parrish and Howe[25] found that their clinical diagnosis of acute glomerulonephritis was confirmed by biopsy in 16 of 18 cases. In patients in whom gross hematuria persists, the diagnosis and prognosis are often uncertain, and renal biopsy is the only means of making a certain diagnosis and of establishing the degree of activity of the disease process. Reubi[21] has pointed out the value of renal biopsy in assessing the activity of the pathologic process in the kidney after the gross hematuria has subsided, but at a time when proteinuria still persists; and the usefulness of biopsy in following those patients who have persistent proteinuria after acute glomerulonephritis is self-evident.

In all these situations, study of the renal biopsy helps to formulate a prognosis which, from the long-term point of view, depends on the number of glomeruli involved and the degree and progression of the glomerular damage. Approximately 85 per cent of patients with acute hemorrhagic glomerulonephritis are said to recover completely from a first attack. In the remainder, however, the prognosis is said to be universally fatal—after periods varying from weeks to many years. In the acute phase the usual treatment at present is a regimen of bed rest and dietary care. Glomeruli are destroyed because of the extent of the inflammatory reaction and because of the overgrowth of fibrous connective tissue. It seems logical, therefore, to assess the anti-inflammatory effects of ACTH and the adrenal glucocorticoids on the progression of these lesions, and such a study, utilizing serial renal biopsy, is at present under way.

Subacute Edematous Bright's Disease.—The value of renal biopsy in the diagnosis of the nephrotic syndrome has been mentioned. Howe[4] was able to make a precise diagnosis in all 22 cases studied by him. Of the first 56 patients with nephrotic syndrome studied by us, an exact histologic diagnosis was made by renal biopsy in 50. The histologic diagnoses are set forth in Table II.

In the past it has been very difficult to give a prognosis on clinical grounds in patients ill with the nephrotic syndrome. Persistent hypertension and considerable azotemia portended a gloomy outlook, but in many cases physicians have had to resign themselves to following the progress of the patient. Renal

TABLE II. HISTOLOGIC DIAGNOSES MADE BY RENAL BIOPSY IN 56 ADULT PATIENTS WITH THE NEPHROTIC SYNDROME

Subacute glomerulonephritis (membranous or proliferative)	16
Diabetes mellitus (diffuse diabetic glomerulosclerosis)	12
Systemic lupus erythematosus (lupus nephritis)	10*
Nephrotic syndrome with predominant tubular degeneration	6
Chronic glomerulonephritis	3
Renal vein thrombosis	2†
Primary amyloidosis	1
Normal (biopsies made after diuresis)	3
Inadequate tissue	2
Diagnosis uncertain	1

*Of these patients 3 had the pseudonephrotic syndrome.[6,24]

†In one case the diagnosis was not made by renal biopsy. As a result of experience gained with this patient, the diagnosis was made by biopsy in the second case.

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biopsy has radically altered this situation. In our experience the outlook has depended in general upon the extent and severity of the glomerular involvement, but we have not yet had enough experience to make exact prognostications after examining a single biopsy section. Those patients in whom glomerular involvement was extensive when first studied have run a downhill course. They have not responded to treatment with corticotrophin or cortisone, nor have other therapeutic measures been successful. Some of them have eventually had a spontaneous diuresis and have thereafter gone into the phase of chronic renal failure with increasing azotemia and death in uremia. In 6 patients, however, there was little or no structural damage to the glomeruli when they were first studied. After eighteen months we have observed that slight thickening of the glomerular basement membrane developed in one 65-year-old patient. She is now in good health. The other 5 patients are all in excellent health, and when last studied no abnormalities were found in their glomeruli. They had been treated with corticotrophin or cortisone with an excellent diuresis. Following diuresis they have *not* developed azotemia. It is too early to foretell whether these patients will make a complete recovery or eventually develop chronic renal disease.

Chronic Nonedematous Bright's Disease.—In addition to the difficulties of making an exact diagnosis in patients with chronic Bright's disease, it is important to establish whether or not the kidney is the seat of an infection, for this is one of the few remediable conditions in the patient with chronic Bright's disease. In our experience, the kidney already damaged by glomerulonephritis is in some cases the site of a superimposed bacterial infection, which may cause further deterioration of kidney function and renal reserve. These infections of the kidney have been detected by culture of the kidney biopsy tissue and by study of the histologic changes seen in the sections (Table I and Figs. 9 to 12).

One other group of patients merits our attention; namely, those in whom persistent proteinuria is found by routine examination. As King[26] has shown, the proteinuria is due most commonly to an underlying glomerulonephritis, pyelonephritis, or congenital anomaly. Orthostatic proteinuria may be as-

Fig. 9.

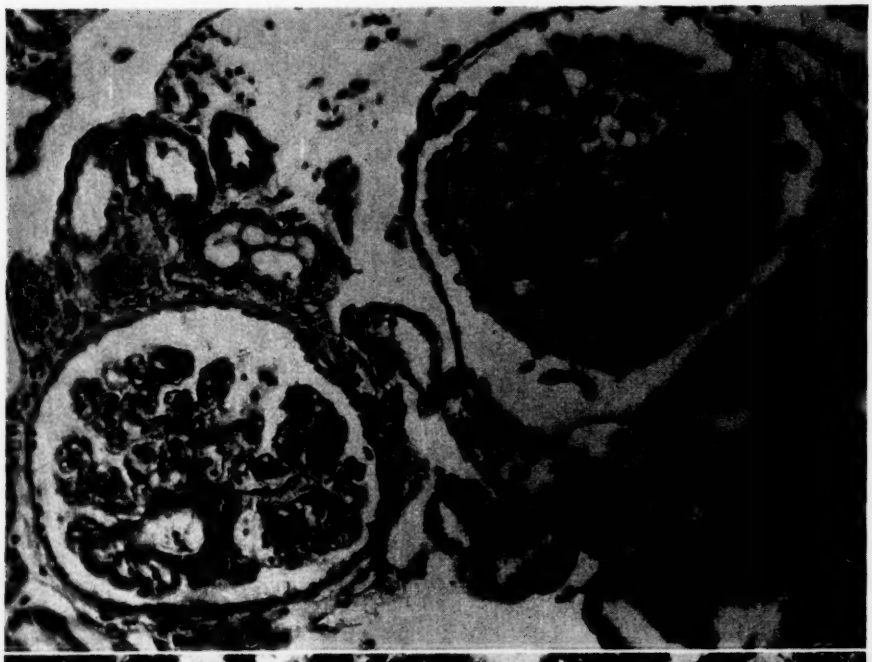

Fig. 10.

Fig. 9.—First biopsy, May, 1954. There is a diffuse hypercellularity of the glomerular tuft. Note the epithelial cell proliferation and some early adhesions between the tuft and Bowman's capsule. (Hematoxylin and eosin × 350; reduced ⅓.)

Fig. 10.—Second biopsy, July, 1954. There is only slight hypercellularity of the glomerular tuft. Note the marked tubular degeneration. (Hematoxylin and eosin × 500; reduced ⅓.)

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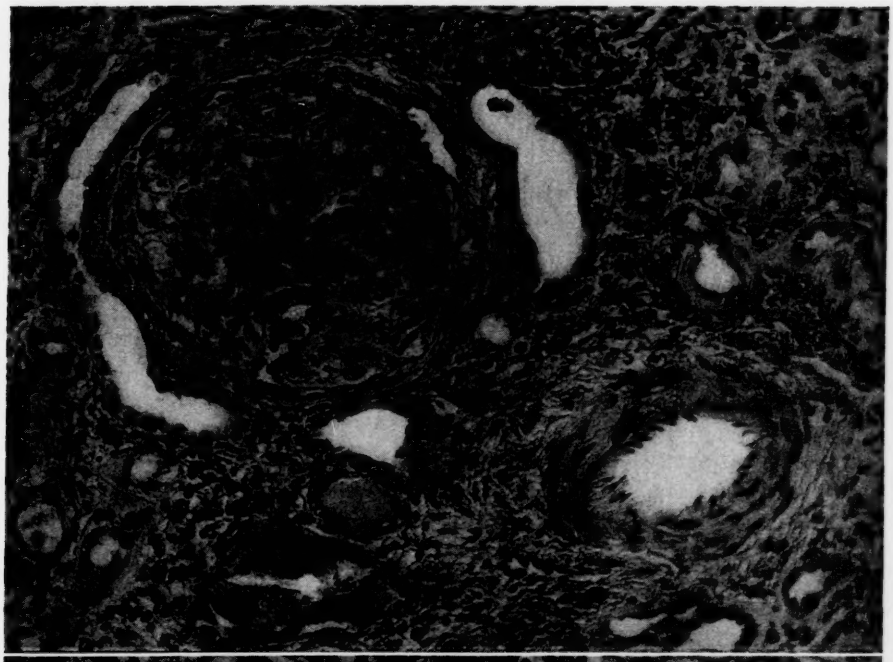

Fig. 11.

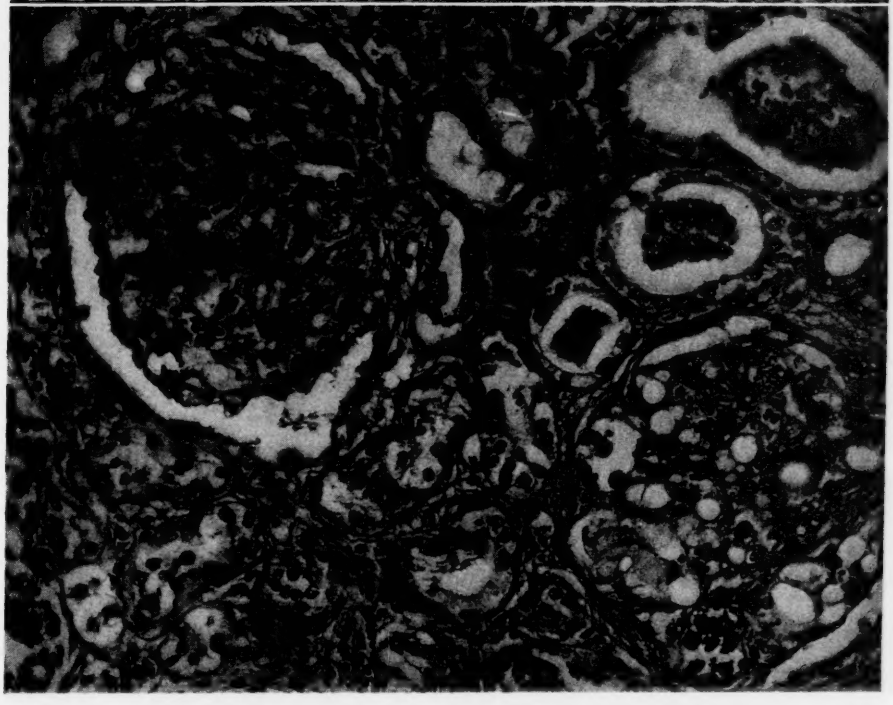

Fig. 12.

Fig. 11.—Fourth biopsy, January, 1955. This glomerulus is almost completely hyalinized and there is fibrous thickening of Bowman's capsule. Note the severe tubular atrophy, the marked interstitial fibrosis, and the infiltration of the interstitial tissue by large numbers of chronic inflammatory cells. (Hematoxylin and eosin × 350; reduced ⅙.)

Fig. 12.—Autopsy, December, 1955. Note the varying degree of hyalinization in these glomeruli. There is some residual epithelial cell proliferation. There are small calcium deposits in one of the glomeruli. Note the severe tubular damage. In other areas, marked interstitial fibrosis and inflammation were seen. (Hematoxylin and eosin × 325; reduced ⅙.)

sociated with renal disorders which may not be benign. Renal biopsy is the only means by which an exact diagnosis can be made in many of these patients.

THE CLASSIFICATION OF BRIGHT'S DISEASE AND THE VELOCITY OF THE PATHOLOGIC PROCESSES

Many difficulties have mitigated against a uniform classification of Bright's disease acceptable to both clinicians and pathologists. These have included lack of knowledge of the etiologic factors involved and the poor understanding of the clinical and pathologic aspects of the natural history of the disease. In the use of the terms "acute," "subacute," and "chronic," semantic difficulties have also clouded the issues, as these terms are used in different senses by pathologists and clinicians.

Serial simultaneous studies of the patient and his kidneys by a team of clinicians and a pathologist have shown that the velocity of the clinical changes in the patient frequently does not parallel the velocity of the pathologic changes from acute to subacute to chronic. This seeming lack of correspondence has been a major cause of difficulties with classification in the past. Serial studies of the patient and his kidneys should provide the foundation for a satisfactory classification of renal disease in the future.

For example, it is at present presumed that in many patients with subacute edematous Bright's disease the onset of the nephrotic syndrome has been preceded by an attack of acute glomerulonephritis. However, it is common experience that frequently a history of such an attack cannot be elicited—and it has been tacitly assumed that this attack must have been silent. Although some of these patients may have had a previous attack of acute glomerulonephritis, in others the acute illness may have started just before the onset of edema. In the latter cases the velocity of the pathologic process has been rapid, and histologically their kidneys may present evidence of acute, subacute, or chronic glomerulonephritis.

FUNDAMENTAL STUDIES IN GLOMERULONEPHRITIS

Renal tissue obtained by biopsy is fresh and can be fixed or frozen instantaneously. Thus, studies can be made on specimens of kidney tissue which have not been changed by post-mortem autolysis and by preterminal anoxia. The fact that renal tissue can be taken at any given stage in the development of the disease, and that tissue can be obtained serially, opens up immense possibilities for future fundamental studies.

Intrarenal Infection.—The application of renal biopsy studies to the diagnosis and etiology of pyelonephritis has been demonstrated by Kipnis and his colleagues.[27] However, it is becoming increasingly apparent that infection within the kidney occurs in a wide variety of renal diseases. For example, we have reported that the kidney may be the site of a primary subacute bacterial nephritis.[9] In these 5 cases there was no bacilluria or bacteremia, but organisms were cultured from the kidney by renal biopsy. All these patients, in whom diagnosis was not possible by conventional means, improved rapidly after treatment with large doses of the appropriate antibiotic.

The exact role of secondary infection in the natural history of noninfective diseases is at present far from clear, but it seems probable that an active inflammatory process in the interstitial tissue leads to further tubular atrophy and interstitial fibrosis and to a further decrease in an already compromised renal function. The role of infection in the development of accelerated hypertension is presently under study, and several cases have been discovered in which an unsuspected interstitial infection appears to have been associated with the development of accelerated hypertension.[9]

Percutaneous needle biopsy of the liver has played a significant part in establishing the relationship of virus infections to hepatic diseases. We have seen a number of patients in whom there was extensive interstitial inflammation in the renal biopsy section, but bacterial cultures of the kidney were negative. Virus infections affect almost all organs in the body, and there is every reason to assume that the kidney is no exception. Studies are at present under way, in cooperation with Dr. Geoffrey Rake of Philadelphia, in an attempt to learn whether some infections of the kidney are indeed due to viruses.

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Histochemistry and Cytochemistry.—The application of histochemical studies to the kidney is still in its infancy. The development by Hotchkiss[28] and McManus[29] of the periodic-acid-Schiff reaction for 1-2 glycol groups in tissues has made possible a more precise study of the anatomy of the glomerular basement membrane. In studying renal biopsies, the use of the P. A. S. stain has allowed us to differentiate clearly between membranous changes in the glomeruli and the apparently normal glomeruli of the nephrotic syndrome associated with predominant tubular degeneration ("lipoid nephrosis") and to show that the changes in the glomeruli of patients with pre-eclampsia are not due to the thickening of the basement membrane.[30] The potential value of histochemical studies on renal tissue was recently reviewed by Wachstein,[31] but the detailed application of these techniques to renal biopsies has not yet been established. In one patient, Bjørneboe and his colleagues[17] have shown that alkaline phosphatase, absent in the edematous phase of the nephrotic syndrome, appeared in the tubular epithelial cells after diuresis. The potential value of such studies was clearly recognized by McManus,[32] who wrote: "A combination study using classical and high magnification morphology, histochemistry, especially the enzyme methods, and clinical studies with renal biopsy seem to me certain to elucidate kidney structure and function." The importance of such studies in the elucidation of tubular function in conditions such as the deToni-Fanconi syndrome, familial renal glycosuria, and salt-losing nephritis, as well as in glomerulonephritis, is obvious.

Using the technique of nephron dissection, Darmady and Stranack[33] have described the "swan neck" abnormality of the proximal convoluted tubule in the deToni-Fanconi syndrome and a similar abnormality in the proximal tubule of patients with congenital familial nephrosis. We are applying the technique of nephron dissection to renal biopsy specimens from patients and the families of patients suspected of having congenital tubular defects. In a biopsy specimen it has not yet been possible to study a complete nephron in continuity; but the glomerulus, proximal convoluted tubule, and descending loop of Henle can

be obtained in continuity (Fig. 13), and the other segments of the nephron can be studied in separate portions. As compared with Oliver's[34] classic work on autopsy specimens, the limitations inherent in the study of biopsy specimens are obvious, for Oliver rightly stresses that the entire nephron should be studied in continuity. Nonetheless, we have confirmed in renal biopsy specimens Oliver's observation that there is differential hypertrophy and atrophy of nephrons in chronic Bright's disease, the hypertrophy being most marked in the proximal convoluted tubule. In chronic Bright's disease the tortuosity of the interlobular arteries became very obvious during dissection; this contrasted sharply with the normal vessel, which is straight and wide and which has short, narrow,

Fig. 13.—Glomerulus and proximal convoluted tubule from a normal kidney. Specimen obtained by renal biopsy and dissected according to the technique of Oliver.[34]

afferent arterioles arising at right angles from it. Pappenheimer[41] has shown that this unusual vascular arrangement in the normal kidney plays an important part in the filtration of blood by the glomeruli by distributing serum and erythrocytes in different proportions to different nephrons. It would seem that the distortion we have observed in chronic Bright's disease would upset this mechanism.

The microfluorescence technique, described by Coons and Kaplan,[35] for the detection of antigens has been used by them to demonstrate protein antigens and homologous plasma proteins in tissues and cells. This technique can be applied to specimens of kidney obtained by renal biopsy and will be of value in demonstrating the site of localization and the nature of antigens in the kidney

in glomerulonephritis in man. It can also be used to demonstrate the site of albumin and globulins in normal and abnormal kidneys.

The great progress made recently in the exploration of the anatomy, physiology, and pathology of the cell has been reviewed by Cameron[36,37]; and techniques applicable to the study of the histochemistry and enzymology of single cells have been described by Lowry and his co-workers.[38,39] Serial studies on the biochemistry and enzymology of normal and abnormal human renal cells are now possible.

CONCLUSION

One hundred and thirty years ago, Richard Bright first correlated clinical and pathologic data on the disease which bears his name. Since that time the combined clinical and pathologic study—in the hands of Volhard and Fahr, Christian, Ellis, and many others—has played a considerable role in advancing knowledge in this field. The development of percutaneous renal biopsy opens a vast new field for clinicopathologic study and for clinical investigation. We are able now to define more precisely the pathologic changes underlying the clinical features of Bright's disease and to make more exact diagnoses during life than were previously possible. By renal biopsy studies we are learning to predict more exactly the prognosis in the individual patient and are learning when and how to treat particular syndromes. A start has been made in the detailed clinical, functional, and pathologic study of the natural history of kidney diseases; and the significance of recurrent attacks, superimposed infection, and the development of hypertension is being evaluated in the light of biopsy material.

The development of modern techniques in microbiology, histochemistry, cytochemistry, electronmicroscopy, and nephron dissection gives us new tools with which to work. All these techniques are already being applied to the study of serial renal biopsies.

Studies made in the past have raised doubts as to the homogeneous nature of the entity known as glomerulonephritis. In 1948, for example, Davson, Ball, and Platt[40] were able to split off a group of patients with periarteritis nodosa. Our studies of the kidney in systemic lupus erythematosus have shown that there is a distinct form of glomerulonephritis in that protean disease[6,24] and suggest that, in the past, cases of "lupus nephritis" have been diagnosed both clinically and pathologically as glomerulonephritis. Further biopsy studies, including the application of new techniques to biopsy material, should help to differentiate other entities included at present under this diagnosis.

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PHYSIOLOGIC ASPECTS OF GLOMERULONEPHRITIS

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INTRODUCTION

THE production of urine by the kidney was postulated by Cushny to result from glomerular filtration and renal tubular reabsorption. Later, Richards with Walker, using micropuncture techniques, demonstrated filtration and reabsorption in the nephrons of the frog. Shortly thereafter, Marshall proved the occurrence of tubular excretion. During the past twenty-five years, methods have become available which quantitatively measure rates of glomerular filtration, renal blood flow, tubular reabsorption, and excretion. These methods and resultant concepts, developed for the most part by Smith and Shannon, have yielded invaluable information about renal physiology. By applying these methods to the study of renal disease in man, physicians have obtained a clearer and broader understanding of the disturbances in physiologic processes caused by anatomic and probably also by biochemical lesions. It is the purpose of this paper to review what is now known about the deranged physiologic processes of the kidney as they occur in glomerulonephritis and, as far as possible, to explain changes in the blood and tissues in terms of abnormalities in kidney function.

The methods described by Smith and his co-workers in the dog have been applied to man by Smith, Goldring, and Chasis. As a result of their work, we now have quantitative physiologic information concerning rates of glomerular filtration, total renal blood flow, and maxima for reabsorption and excretion of certain substances. Some of the rates are defined as follows:

The *clearance* of a substance is defined as the rate at which the substance is cleared from the plasma by the kidney per unit of time. The glomerular filtration rate (GFR) is defined as clearance by filtration only, without tubular

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subtraction or addition. Inulin is filtered in this manner. The clearance of inulin, or of any other substance, is calculated as follows:

$$C\ \text{inulin} = \frac{U\ \text{inulin} \times V}{P\ \text{inulin}}$$

where

C inulin = clearance of inulin, defined as the volume of plasma required to filter the quantity of inulin excreted in the urine in one minute. Since inulin is only filtered without tubular action, the clearance rate is equal to the glomerular filtration rate (GFR).

U inulin = Urine concentration (mg./c.c.)

V = urine flow (c.c./min.)

P inulin = Plasma concentration (mg./c.c.)

If a substance is reabsorbed by the tubules, the clearance will be less than that of inulin; if it is excreted by the tubules, the clearance will be greater than that of inulin.

The clearance of p-aminohippurate (PAH) or of Diodrast (D) is much greater than that of inulin. Except for the amount delivered to supporting structures, the kidney clears all of these substances that are delivered to it in each circulation. The clearance of these substances is therefore equal to the rate of renal plasma flow (RPF).

The filtration fraction (FF) is defined as the fraction of plasma delivered to the kidney (RPF) which is filtered at the glomeruli. This is calculated by dividing glomerular filtration rate (GFR) by the rate of renal plasma flow (RPF):

$$\text{Filtration Fraction} = \frac{GFR}{RPF} \times 100$$

When sufficient glucose is filtered and delivered to the proximal convoluted tubules, the maximal rate of glucose reabsorption (T_{mG}) can be calculated. The rate of delivery of the substance to the tubules is calculated by multiplying the plasma concentration (P) of the substance by the glomerular filtration rate (GFR). For glucose this is $P_{\text{Glucose (mg./c.c.)}} \times C_{\text{Inulin}}$. The rate of glucose excretion in the urine is U glucose × V, where U glucose = Urine concentration of glucose (mg./c.c.) and V = urine flow (c.c./min.). If we know the rate of glucose excretion, we can calculate the rate of reabsorption per minute. At high plasma levels of glucose when maximal reabsorption takes place this is:

$$T_{mG} = P_G \times C_{In} - U_G V$$

where T_{mG} = Rate of reabsorption of glucose (mg./min.).

Maximal tubular excreation is calculated from the maximal rate of excreation of Diodrast (D) or PAH at high blood levels of these substances. The calculation involves the rate of PAH excretion in the urine ($U_{PAH}V$) and the amount of PAH filtered. The total amount of PAH excreted in the urine is the sum of filtered PAH and of the PAH excreted by the tubules. Therefore, the calculated quantity filtered is subtracted from the total excreted in the urine. A correction factor (f) for the small amount of PAH bound to plasma proteins

and therefore not available for filtration is applied. Thus, where T_{mPAH} = maximum amount excreted by the tubules (mg./min.), $T_{mPAH} = UV_{PAH} - fP_{PAH} \times C_{In}$.

Tubular maxima are generally interpreted as measures of tubular mass (T_m) provided certain assumptions discussed later can be made. Since reabsorption can take place only if glomeruli are delivering material to each corresponding tubule for reabsorption, maximal tubular reabsorption is a measure of the number of functioning *complete nephrons*. Maximal tubular excretion also can be a reflection of functioning *tubules*. However, in order to excrete a substance glomeruli need not be functioning, since compounds can be delivered to the tubules and transported into the tubular lumina independently of filtration.

The approximate normal values in man, corrected to a surface area of 1.73 sq. mi. for the above functions are:

C_{In} (GFR) = 130 c.c./min.
C_{PAH} (RPF) = 700 c.c./min.
F. F. (Filtration Fraction) = 18.7 per cent.
T_{mPAH} (Excretory T_m) = 80 mg./min.
T_{mG} (Reabsorptive T_m) = 300 mg./min.

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RENAL HEMODYNAMICS IN GLOMERULONEPHRITIS

Glomerular Filtration and Renal Plasma Flow.—The principle anatomic lesion of acute glomerulonephritis occurs in the glomeruli. These changes usually consist of a thickening of the basement membrane and increased cellularity of the tufts. There are no consistent changes in the arterioles. It is not surprising, therefore, that the greatest functional change is observed in the glomerular filtration rate.

The inulin clearance (GFR) is variably reduced in almost all cases of acute nephritis. The renal plasma flow, as measured by PAH or Diodrast clearances, is less affected. Although it is usually decreased, the reduction in plasma flow is not as marked as the reduction in the glomerular filtration rate. This disproportion between changes in filtration rate compared to those in renal plasma flow lowers the filtration fraction (FF).[1] The low filtration fraction is characteristic of glomerulonephritis.[1-4]

As the disease progresses to the chronic state, the glomerular circulation is gradually obliterated, tubular tissue is destroyed, and arteriolar lesions become evident. In chronic nephritis, nephrons differ from one another in structure and probably also in function. Some tubules become hypertrophied and others atrophied. Vascular channels develop between the capillary circulations of adjacent tubules, so that the blood supply is probably shared.[5] GFR and RPF are now greatly reduced. The FF remains low.[1]

In far-advanced disease there is such severe damage to nephron organization that measurements of renal plasma flow by the clearance techniques are not valid, and a correction has to be made to allow for decreased renal extraction. The clearance of substances measuring renal plasma flow depends on the fact that normally the compound is almost totally cleared during each circulation

by the filtering and secreting tissues of the kidneys. Therefore, plasma in the renal vein should contain only the small amounts of the test substance which have perfused through nonexcretory tissue of the kidney. The extraction ratio of a substance is calculated from values obtained for arterial and renal venous blood concentrations:

$$E_{PAH} = \frac{\text{Arterial concentration} - \text{Venous concentration}}{\text{Arterial concentration}}$$

In normal subjects the extraction value, E_{PAH}, is reported to be 0.91.[6] Cargill[3] reports E_{PAH} in eight patients with chronic nephritis as 0.84 when C_{PAH} was 455 ml./min. or more. He found an E_{PAH} of 0.64 to 0.35 in three patients whose C_{PAH} ranged from 293 to 90 ml. He concluded that E_{PAH} does not decrease until the C_{PAH} is below 300 ml./min. Bradley, Curry, and Bradley[6] report that E_{PAH} is reduced in both acute and chronic glomerulonephritis. The low E_{PAH} in renal disease indicates that blood passes from the arterial to the venous side without contact with active transport sites. In glomerulonephritis, therefore, clearances for PAH or Diodrast below 300 ml./min. should be corrected for the decreased extraction. The extraction ratio must be determined for each individual patient. Before extraction ratio data were available, Earle, Taggart, and Shannon[1] believed that poor extraction was probable and, therefore, concluded that the very low Diodrast clearances they observed in chronic glomerulonephritis were not valid.

Although the over-all renal plasma flow in nephritis is generally reduced, plasma flow per unit of excretory tissue is usually normal or even increased. This conclusion is based on calculation of the ratio of the clearance of Diodrast to the tubular excretory maximum for Diodrast (T_{mD}). The T_{mD} is interpreted as a measurement of active tubular mass, so that the ratios C_D/T_{mD}, or RPF/T_{mD} yield a value for blood flow per functional unit of tubular tissue. Earle, Taggart, and Shannon[1] reported a normal value of 13.4, $\sigma = 1.4$. Most of the patients with acute and chronic disease had normal or supernormal values. Relating the filtration rate to T_{mD} (GFR/T_{mD}) yields an index of glomerular filtration per unit of tubular mass. As would be predicted from the predominant glomerular lesion, this ratio is characteristically low in nephritis.

Hypertension, which may increase the effective filtration pressure, apparently does not increase the reduced GFR of nephritis,[1] as judged from the observations that the RPF/T_{mD} and GFR/T_{mD} ratios do not differ qualitatively in nephritic patients with or without hypertension.

TUBULAR FUNCTIONS

Excretory T_m.—The maximal excretory T_m for Diodrast or PAH generally is reduced in both acute and chronic nephritis. However, some patinets with acute nephritis have been reported to have normal values for excretory T_m.[1,2,9]

In interpreting T_m data for Diodrast or PAH, the tubular mass as well as the state of the substrate and enzymatic activity of the tubule cells must be considered. Mudge and Taggart[7] demonstrated that the excretory T_m for PAH may be increased by the infusion of acetate or lactate in dogs. It is clear,

therefore, that more than tubular mass and blood supply are involved in the excretory process. The chemical composition of the tubular cells can alter the excretory processes within limits independent of blood supply. Baldwin and McLean[8] showed that sodium acetate increased the T_{mPAH} in normal man as well as in one patient with chronic nephritis and in two patients with essential hypertension. Excretory T_m data should be considered as indicating an effective excretory process which may not only be directly related to the amount of functioning tubular tissue mass, but also dependent on the cellular substrate. It is conceivable that a T_m value may represent a small mass of tubules with a great deal of activity or a large mass with little individual tubule cellular activity.

Reabsorptive T_m.—The glucose T_m may be considered a measure of the number of functioning nephrons,[10] provided the assumption is made that there is no alteration in the tubule cellular substrate affecting the quantity of glucose reabsorbed per minute. An example which cannot be explained without this assumption has been reported in diabetes mellitus.[11]

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Normally, the ratio GFR/T_{mG} expresses the relative proportion of functioning glomeruli to tubules. The ratio remains within normal limits if complete destruction or dysfunction of glomeruli occur. This would occur if the glomeruli were not filtering and, therefore, the attached tubules were not receiving glucose to reabsorb. If only parts of the individual glomeruli were involved and the reabsorptive process were normal, the tubules could receive adequate amounts of glucose and a normal T_{mG} would result. A reduction in GFR with a normal T_{mG} would yield a low GFR/T_{mG}. A high GFR/T_{mG} would result if T_{mG} were reduced out of proportion to a reduction in GFR, presumably due to a defect in the transport mechanism.

In five patients with acute nephritis, studied by Earle, Farber, Alexander, and Pellegrino,[2] GFR/T_{mG} was reduced, but in four others it was normal. In almost all the cases GFR and T_{mG} were reduced. These observations indicate that if no substrate defect is present, some complete nephrons are not functioning when the GFR/T_{mG} ratio is normal. However, in some patients the combination of decreased GFR, T_{mG}, and GFR/T_{mG} ratio indicated that in addition to obliterated glomeruli, glomeruli with diminished filtering capacity were present and that normal tubules were associated with them.

ELECTROLYTES

Sodium.—Patients with acute nephritis develop edema principally as a consequence of sodium and water retention by the kidneys. The most plausible physiologic explanation is that the increased retention of sodium is due to the reduction in GFR.[12] Since over 95 per cent of the filtered sodium is reabsorbed by the tubules and the filtered load is high (GFR 180 L. per day $\times$ serum sodium of 140 meq./L.), a small change in filtration rate can lead to glomerulotubular imbalance with excessive amounts of sodium retained by the kidneys. With the excess sodium, excess water is retained and fluid accumulates as extracellular fluid.

There is, however, related evidence to indicate that the lowered filtration rate in nephritis may not entirely explain sodium and water retention. It has

been observed that spontaneous diuresis is not accompanied by a consistent change in filtration rate.[2] In several of the patients studied, diuresis developed without any increase in the markedly reduced filtration rates.

Burnett, Burrows, and Commons[13] found, in patients with chronic glomerulonephritis without edema or heart failure, a diminished ability to excrete sodium following an intravenous sodium bicarbonate load of 200 to 400 meq. The diminished excretion was related to a lowered clearance of inulin. However, more of the administered sodium was excreted by patients with glomerulonephritis than by patients with nephrosis, although the reductions in GFR were similar. The difference between patients with nephritis and with nephrosis may have been due to the fact that patients with nephrosis have a tubular defect, reducing their ability to reabsorb excess sodium, rather than to the fact that those with nephritis have a better tubular mechanism for the handling of sodium in spite of diminished GFR.

The causes for sodium retention in glomerulonephritis are probably multiple. The excess sodium reabsorbed due to a diminution of filtration rate is probably the dominant mechanism. Other unknown mechanisms, perhaps of hormonal or intrinsic tubular function, play a role in the diuresis following acute glomerulonephritis and in the handling of sodium in the chronic stage of the disease.

Potassium.—Renal mechanisms for the excretion of potassium play an important role in regulating the plasma potassium level. In glomerulonephritis, high levels of potassium can occur in the extracellular fluid and at times may reach lethal concentrations. In general, the potassium level is increased in severe acute glomerulonephritis and at the final stage of chronic glomerulonephritis. Increased potassium level is most often related to the reduction in filtration rate. Less K is filtered, less is delivered to the kidney for excretion, and the concentration in the plasma rises.[2,12] Until marked oliguria or anuria occurs, the major source of K is in the ingested diet. Even low protein diets usually furnish 50 meq. K per day.

The mechanism of tubular excretion of potassium tends to overcome the effect of the reduction in filtration rate. Berliner and Kennedy[14] demonstrated in dogs that potassium excreted in the urine may exceed the amount filtered when these animals were pretreated with oral KCl and then infused with KCl. This is evidence of tubular excretion of K. Berliner, Kennedy, and Hilton[15] later showed that a similar mechanism exists in normal man.

Leaf and Camara,[16] in a study of four patients with severe chronic renal insufficiency, concluded that tubular excretion of potassium probably plays an important role in prevention of hyperkalemia in renal disease. However, the quantitative aspects of how this mechanism prevents hyperkalemia have not been defined.

Earle, Sherry, Eichna, and Conan,[17] in an intensive study of a patient whose presumptive diagnosis was chronic nephritis, demonstrated a marked hypokalemia that resulted from excess renal loss of potassium. The latter was caused by tubular excretion and led to a negative K balance. During clearance studies, when the daily oral intake of potassium was 104 meq., the ratio of excreted potassium per minute to the filtered K was frequently over 100 and as high

as 194. These observations indicated marked tubular excretion of K. During periods when intake of potassium was 104 meq. per day, the plasma K level was 3 meq./L. or below. Hypokalemia is not rare in renal disease, but normal K levels or hyperkalemia occur more commonly in both acute and chronic glomerulonephritis.

WATER

The physicians of Richard Bright's generation observed that the specific gravity of urine was low in Bright's disease. Volhard[18] introduced the measurement of specific gravity as part of the clinical study of renal function. Later, Fishberg and others devised tests determining the concentrating and diluting capacity of the kidneys; these tests consisted of measuring specific gravity during hydropenia and water diuresis. Clinically, specific gravity values under test conditions have become guides of the stage and degree of renal organic involvement.

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Specific gravity roughly measures concentration, but it does not indicate which of the dissolved solids in the urine is contributing to the measurement. Electrolytes have greater effects on the specific gravity than do organic substances.[19] The measurement of specific gravity may be a useful clinical tool, but it gives no quantitative or physiologic data concerning the renal handling of water and dissolved solutes.

In determining how the kidney handles water in relation to dissolved solutes in the glomerular filtrate, Smith and his co-workers[20,21] recently have measured the osmolar clearance. The osmolar clearance measurement yields definitive quantitative data concerning the concentrating and diluting properties of the kidneys. The urine is probably concentrated in the distal tubules and in the collecting ducts.

Glomerular filtrate at the level of the glomerulus is composed of all the constituents of plasma, except for plasma proteins. Therefore, the concentration of the various components of the plasma is the same in the glomerular filtrate (allowing for Donnan's equilibrium), and the osmotic pressure is equal to that of plasma minus the pressure contributed by the proteins. As the filtrate travels down the tubules, solutes are reabsorbed. Far down in the distal tubule and collecting ducts, additional water may be reabsorbed, producing a hypertonic urine. The rate at which osmotically active substances are cleared from the plasma in cubic centimeters per minute is the osmolar clearance. This clearance is calculated, as are all other clearances from the equation:

$$C\ osm = \frac{U\ osm \times V}{P\ osm}$$

where C osm = osmolar clearance, U osm = osmolar concentration of urine, V = urine flow, c.c./min., and P osm = osmolar concentration of plasma.

When solutes and water are reabsorbed in the same proportion as in plasma, the rate of urine flow (V, c.c./min.) is equal to C osm and the urine is isosmotic with glomerular filtrate. When urine flow per minute is lower than C osm, the urine is hypertonic, as solute free water has been reabsorbed. If urine flow is

greater than C osm, the urine is hypotonic in relation to glomerular filtrate, or plasma and solutes have been reabsorbed in greater proportion than water. Smith postulates that when urine is hypotonic, osmotically active constituents of the urine are absorbed without an equivalent amount of water, leaving "free water" behind. Although it is possible that water is actually excreted into the tubular lumina to make the urine hypotonic, Smith does not believe that this occurs.

When urine is hypotonic, the free water clearance can be calculated by the following formula:

$$C_{H_2O} \text{ (free water clearance)} = V - C_{osm}.$$

When urine is hypertonic, the measurement of water reabsorption is expressed as Tc_{H_2O}. This designates the volume of water that would have to be added per minute to a hypertonic urine to make it isosmotic to plasma. Alternatively, it is the amount of solute free water that is absorbed per minute from the tubular urine that finally yields a hypertonic urine in the bladder. V is now lower than the osmotic clearance, hence the expression, $Tc_{H_2O} = C_{osm} - V$.

Zak, Brun, and Smith[22] observed that at varied urine flows of more than 5 to 7 c.c. per minute and during maximal antidiuresis, Tc_{H_2O} achieved an approximately steady level, which was fairly constant for the individual, of about 5 c.c. per minute per 100 c.c. of glomerular filtrate. This value, calculated as described above, was designated $Tc^{m}H_2O$. Therefore, a fairly constant quantity of solute free water is reabsorbed per minute under conditions of urine flows above the limiting value of $Tc^{m}H_2O$, and under situations of maximum antidiuresis. In two cited experiments, Zak, Brun, and Smith[22] achieved maximal antidiuresis and high urine flows by infusing mannitol, or mannitol plus pitressin, in cases previously made hydropenic.

Baldwin, Berman, Heinemann, and Smith[23] examined the magnitudes of concentrating ability of the tubules by using osmolar clearance tests in five patients with acute and in fourteen patients with chronic glomerulonephritis. The patients with acute nephritis had filtration rates above 60 c.c./min., and Tc_{mH_2O}/100 c.c. G.F. ranging from 5.3 to 8.1. Thus, at these levels of GFR the concentrating ability of the remaining nephrons did not seem to be impaired. When the GFR was below 60 c.c. per minute in the patients with chronic nephritis, different values were obtained. In five instances, the Tc_{mH_2O}/100 c.c. glomerular filtrate was normal, but in eleven the values were 3.0 c.c. or below. It would seem that when the filtration rate is markedly reduced, maximal osmolar concentration does not occur.

The studies of Baldwin and his associates[23] show that in chronic nephritis urine is concentrated until glomerular and tubular dysfunction are far advanced. In several instances, maximal specific gravity was low when Tc_{mH_2O}/100 c.c. of glomerular filtrate was normal, suggesting that specific gravity measurement may not be reliable as an index of concentrating ability. Lack of concentrating ability, as measured by maximal concentration of specific gravity in patients

with advanced renal disease, may be more apparent than real when many nephrons are destroyed. The remaining nephrons are constantly undergoing an osmotic diuresis and are excreting dilute urine, as measured by specific gravity, but the rate of water reabsorption per nephron may be normal, as evidenced by a normal $T_{c_{mH_2O}}$ /100 c.c. glomerular filtrate.

The diluting mechanism has not yet been systematically investigated. Other factors that may be concerned with water and solute excretion include protein and solute intake. The relationship of these variables to renal functions has not been clearly defined and will undoubtedly be investigated in the future.

UREA CLEARANCE

Plasma urea increases in acute and chronic nephritis when renal impairment is moderate to severe. The increase in the plasma urea level is related to the reduction in glomerular filtration rate.[2,12]

Normally, the urea clearance is lower than the inulin clearance. As urine flow is increased by producing a water or osmotic diuresis, urea clearance increases. From these and related observations, it has been postulated that urea is filtered and then passively reabsorbed along with water by the tubules.[25,26] In chronic nephritis with reduction in filtration rate, the urea clearance is depressed in proportion to the decrease in inulin clearance and the ratio of urea to inulin clearance remains the same. However, as kidney damage progresses, the absolute value of the urea clearance approaches the inulin clearance. Since less of the filtered water is reabsorbed, less urea is also reabsorbed. The decreased urea clearance in renal disease may be explained not only by a low GFR but also by backward diffusion of urea through damaged tubule cells. If the latter occurs, low urea clearance would not be directly related to water reabsorption. Chasis and Smith[25] found no evidence of increased back diffusion of urea in patients with chronic glomerulonephritis. Earle, Farber, Alexander, and Pellegrino[2] found that the relation of urea clearance to inulin clearance and urine flow was not constant in subjects with acute nephritis. In some patients, the urea clearance increased during recovery when the inulin clearance remained unchanged, so that the ratio of urea to inulin clearance increased. It was postulated that increased back diffusion of urea through damaged cellular membranes might occur in acute nephritis. With reconstitution of the renal epithelium, urea reabsorption proceeds as it normally does. Sirota[27] also found evidence of back diffusion of urea in patients with acute renal failure. These observations suggest that perhaps the presently accepted concepts of tubular reabsorption of urea may not be completely valid. Mechanisms other than passive reabsorption may be unmasked by observations made in disease states.

As a rule, the abnormal physiologic functions so far discussed in acute nephritis return toward normal after diuresis has occurred. Prognosis, however, cannot be made on the basis of such observations. During exacerbations in chronic nephritis, the same diminution in function takes place with subsequent return toward the level of renal function that existed before the acute flare-up.[28]

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PROTEINURIA

The problem of proteinuria[29-33] has been actively investigated since electrophoretic techniques have become available. Most of the reported studies related to proteinuria in renal diseases concern the characterization and quantitation of urinary proteins in nephrosis. Few studies have been done on urine from patients with acute or chronic glomerulonephritis.

Blackman, Goodman, and Buell[34] examined the urine of patients with acute or chronic glomerulonephritis and attempted to correlate the pathologic changes in the glomeruli with the chemically determined albumin and globulin content of the urine. Their study was not extensive but indicated that changes occur in the quantity of protein excreted and in the globulin fraction in the urine of patients with acute nephritis of varied severity.

Protein excretion was not great during the acute phase in patients who subsequently recovered. The concentration of protein was less than 0.5 Gm. per 100 c.c. and less than 35 per cent of the total urinary protein was globulin. The severer the disease as judged by pathologic examination, the more proteinuria occurred and the greater was the percentage of globulin found in protein of the urine. In progressive renal failure, variations in protein and globulin content occurred. When renal disease was far advanced, the protein content and the globulin content of urine were moderate. The latter observation is not surprising and is probably related to the massive destruction of nephrons at this stage of the disease.

Leutscher[35] obtained an electrophoretic analysis of the protein in the urine of three patients with glomerulonephritis in uremia and found a larger percentage of albumin than of globulin.

Sellers and Marmorston[36] examined by paper electrophoresis the proteins in the urine of patients with various forms of renal disease, including chronic glomerulonephritis. Except in cases of acute renal failure and multiple myeloma, the predominant protein fraction was albumin, which was greater than the combined globulin fractions. There was a good deal of variation in the percentage of the various proteins in different patients, and no characteristic electrophoretic pattern was obtained.

Lathem, Roof, Nickel, and Bradley[37] investigated the effect of orthostasis on renal hemodynamics and the protein excretion in patients with renal disease. Among their subjects were four patients with acute and six with chronic glomerulonephritis. During orthostasis, there was a decrease in GFR, RPF, T_{mG}, and protein excretion. They attributed these changes to generalized vasoconstriction without alteration in glomerular capillary permeability. Paper electrophoretic studies disclosed considerable variation in the character of urinary proteins. In one patient with terminal uremia and nephritis the protein was almost all albumin, in another with less renal impairment the urinary protein pattern was similar to that of the plasma.

Hardwicke and Squire[38] have recently presented data to indicate that serum proteins are reabsorbed from glomerular filtrate and that this process is not selective in regard to the different protein fractions. They have postulated that the fractions are reabsorbed by a competitive process. Following the

infusion of human serum albumin into four patients with renal disease, the clearances of the globulin fractions rose in proportion to an increase in albumin clearance. This occurred when there was no rise in the concentration of serum globulin. When the clearances of the globulin fractions are expressed as percentages of the albumin clearance, variations that occurred could be due to alterations in glomerular permeability. These variations in renal disease suggest that changes in pore size of the glomeruli play a role in the pathogenesis of proteinuria in renal disease. In addition, there is also a diminution in tubular reabsorption of proteins.

It is still uncertain how proteins are handled by the kidney. Some feel that proteins appear in the urine only when glomerular permeability is increased. Others believe that proteins are normally filtered and reabsorbed by the tubules.[30] Unquestionably, with proper techniques, proteins are found in normal human urine. Rigas and Heller[39] noted that the normal excretion of total protein is 39 mg. per 24 hours, 14.8 mg. of albumin, and 25.8 mg. of globulin. Mucoproteins, glycoproteins, and a polysaccharide were also found. McGarry, Seton, and Rose,[40] using more refined precipitation techniques, stated that normal protein excretion was 71 mg. per day with an albumin to globulin ratio of 0.65. The mechanism for the handling of these large molecules by the kidney undoubtedly will be actively investigated in the future. The physical properties of the proteins and the glomerular membranes as well as tubular functions presumably contribute to the excretion of protein. When these variables are better understood, it may then be possible to correlate the current varied observations on proteinuria with clinical conditions.

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WATER AND ELECTROLYTE DISTRIBUTION

The causes for edema in acute glomerulonephritis are not completely known, but a major role in the expansion of extracellular fluid volume is the renal retention of sodium and water. The sudden onset of facial edema without dependent edema has led observers to postulate an increase in capillary permeability, with subsequent leakage of protein and water from the vascular fluid. The earlier measurements of edema fluid indicated that the fluid was high in protein content. However, Warren and Stead[41a] reported that the protein content of edema fluid from patients with acute nephritis was about 0.5 Gm. per cent, similar to the protein content of the edema fluid of congestive heart failure. The latter findings argue against increased capillary permeability. However, representative samples of edema fluid from patients with massive edema are difficult to obtain. If analysis is to be definitive, edema fluid should be taken from close to the capillary bed since dilution of fluid may occur as it approaches the subcutaneous tissue. Analysis of extravascular fluid obtained from the face might be of greater value.

In chronic nephritis, edema is usually minimal or absent except in the presence of an exacerbation, subacute nephritis, or heart failure secondary to hypertension. Many patients with chronic nephritis succumb without edema.

Extracellular and Intracellular Distribution of Water and Electrolytes.—The detection of edema on physical examination is evidence of the extracellular

accumulation of electrolytes and water. The concentration of electrolytes in edema fluid has been measured and proved to be about the same as in plasma, allowing for the Donnan equilibrium. It is more difficult to ascertain the possible changes in electrolyte concentration which may occur within cells associated with extracellular fluid accumulation. If methods were available for accurately measuring extracellular fluid volume in edematous states, an estimate of intracellular concentrations could be obtained by employing measurements of total body water, extracellular fluid volume, and total body electrolytes. Thus, if extracellular fluid volume was available, calculations of the extracellular quantities of sodium, potassium, and chloride could be attained by multiplying the concentration of these electrolytes in serum (minus the Donnan factor) by the volume of the fluid. Subtracting the total extracellular electrolyte content in milliequivalents from the total body electrolyte content would yield a value for total intracellular electrolyte. The intracellular fluid volume could be obtained by subtracting extracellular fluid volume from total body water. It would then be possible to calculate intracellular concentration in milliequivalents per liter by dividing intracellular electrolyte content by intracellular fluid volume.[41b] The calculations as described do not account for electrolytes in solid or semisolid tissues. Unfortunately, calculations of this sort are not feasible in edematous states, for there is no adequate method available for the measurement of extracellular fluid volume in edematous patients.

Farber and Soberman[42] attempted to determine sodium distribution in various edematous states by calculating the body electrolyte concentration in terms of milliequivalents per liter of body water, employing total exchangeable body sodium and body water determinations. They found that patients with edema had increased concentration of body sodium. This is expected, since the concentration of sodium in extracellular fluid is greater than in other tissues or compartments of the body. The sodium content of the body would, therefore, increase 140 meq. for each liter of increase in water, which is a disproportionate increment as related to body water (Theoretical Calculation, Table II). The rise in body sodium concentration in patients with edema due to renal disease (acute nephritis and nephrosis) corresponded to the expected increase in extracellular fluid (Table I).

It was, therefore, concluded that the increase in body sodium in the patients with nephritis could be accounted for on the basis of extracellular fluid accumulation alone. No change in intracellular or solid tissue composition of sodium had to be postulated. In patients with heart disease, there was a high ratio of body sodium to body water which could not be explained as caused by simple extracellular fluid accumulation (Table I, Table II). These considerations led to the presumption that sodium is present in excess outside of the extracellular fluid compartments, perhaps in cells, connective tissue, bone, or cartilage. Other changes in patients with heart disease, including intracellular water loss (Table II), must also be considered as possible contributing factors to this increased ratio. These changes in intracellular water probably play a role in increasing the sodium-water ratio in edematous patients with heart disease, but it is not

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TABLE I. BODY WEIGHT, BODY WATER, AND TOTAL EXCHANGEABLE SODIUM. SUMMARY OF MEAN VALUES

	NORMAL SUBJECTS CONTROLS	EDEMATOUS CARDIACS	NONEDEMATOUS CARDIACS	HEPATIC DISEASE	RENAL DISEASE
Weight (Kg.)	66.8	68.2	63.7	70.0	65.8
Body water (L.)	35.0	37.9	34.2	43.0	43.2
B. W./Kg. (% of body wt.)	52.0	55.5	54.2	61.0	65.0
Total exchangeable sodium (meq.)	2896	4036	3362	3810	3228
TENa/B. W. (meq./L.)	81.3	108.2	100.4	90.3	89.2
TENa/Kg. (meq./Kg.)	43.7	59.9	53.5	56.2	57.9
Number of subjects	27	50*	33*	16*	10

TENa—Total exchangeable sodium as measured by isotope dilution.
B. W.—Body water as measured by antipyrine dilution.
*In the edematous cardiac, nonedematous cardiac and hepatic groups there were 4, 1, and 2 patients, respectively, whose weights were not obtainable.

TABLE II. THEORETICAL CALCULATIONS OF THE RELATIONSHIP OF BODY WATER, BODY WEIGHT AND TOTAL EXCHANGEABLE SODIUM

	WEIGHT (KG.)	BODY WATER (L.)	PER CENT BODY WEIGHT	TENa
CONTROL				
Serum Na = 140 meq./L. (assumed for all calculations)	67.0	35.0 TENa/A.S. = 82.5 TENa/Kg. = 43.7	53.0	2896
WEIGHT LOSS				
10 Kg. loss in form of protein, or 7.5 L. of intracellular water loss	57.0	27.5 TENa/A.S. = 105.0 TENa/Kg. = 50.9	48.2	2896
10 Kg. in form of fat	57.0	33.0 TENa/A.S. = 88.0 TENa/Kg. = 51.0	58.0	2896
10 Kg. in form of protein, or 7.5 L. of intracellular water plus gain of 10 L. of extracellular fluid	67.0	37.5 TENa/A.S. = 114.0 TENa/Kg. = 64.0	56.0	4296
WEIGHT GAIN				
10 L. of extracellular water	77.0	45.0 TENa/A.S. = 95.2 TENa/Kg. = 55.8	58.5	4286
15 L. of extracellular water	82.0	50.0 TENa/A.S. = 100.0 TENa/Kg. = 61.0	61.0	4996

TENa/A.S.—Total exchangeable sodium per liter of body water as measured by antipyrine dilution.
TENa/Kg.—Total exchangeable sodium per kilogram of body weight.

necessary to assume that these variables are factors contributing to the moderately increased ratio in the patients with massive edema due to renal disease.

Hyperkalemia is a common occurrence in both acute and chronic nephritis. Increased plasma potassium is more common in the late stage of chronic nephritis and at times reaches toxic levels. The rise is related to the low GFR. Elkinton, Tarail, and Peters[43] found elevated serum potassium in twelve of eighteen patients twenty-four hours before death from chronic nephritis. In these patients, the serum potassium rose when urine output reached oliguric levels. The above authors present daily balance data based on intake and output to indicate that a net transfer of potassium from cellular to extracellular phase takes place in patients with terminal glomerulonephritis. In only a few instances did some of the ingested potassium of the diet enter the cells. Normal cells would be expected to take up potassium which enters the blood stream following ingestion. The observations that cells of patients with terminal nephritis do not take up potassium suggest that cellular metabolism may be altered.

Acidosis associated with nephritis is due to several renal factors. The reduced glomerular and tubular function causes sulfate and phosphate to accumulate in the blood and displace bicarbonate. There is at times some renal loss of sodium because of glomerulotubular imbalance. This loss is related to the osmotic tubular diuresis in patients with low filtration rates. The diuresis reduces the time during which the glomerular filtrate is in contact with the tubular cells and thus may reduce sodium reabsorption. The acidosis may be further aggravated by diminished ammonia production. This base-saving mechanism is reduced because of loss of the tubule cells which produce ammonia and may also be related to glutaminase inactivation.

Calcium usually falls as a result of the rise of inorganic phosphorus in the blood.[44,45]

The only available data concerning cellular composition in the acidosis associated with renal insufficiency are those of Mudge and Vislocky.[46] Their patients did not have glomerulonephritis but had chronic renal acidosis without glomerular insufficiency, as described by Albright. Analysis of muscle biopsies, assuming that chloride was extracellular, showed a decrease of intracellular potassium and an increase in intracellular sodium. Whether these changes occur in other types of acidosis has not as yet been established.

CARDIOVASCULAR HEMODYNAMICS

Many investigators have observed that patients with glomerulonephritis may also have congestive heart failure. The reported incidence of heart failure varies from 17 per cent by Murphy[47] to 71 per cent by Whitehill.[48] In a series of 12 edematous patients, LaDue[49] found evidence that all had "right heart failure." Peters[50] analyzed the records of 291 patients and concluded that the "chief disorder responsible for edema in acute glomerulonephritis is congestive heart failure." These observers based their conclusions on signs and symptoms usually observed in congestive heart failure, that is, dyspnea, orthopnea, râles in the lungs, hepatomegaly, edema, and an increased heart size.

The data of LaDue[49] and Peters[50] demonstrate one fairly constant difference between classical heart failure and the failure in nephritis. A normal circulation time was characteristic in the patients with renal disease who had signs of circulatory congestion. The circulation time is usually prolonged in congestive heart failure.

It has been thought that the causes of heart failure in glomerulonephritis may be hypertension and/or myocarditis. LaDue felt that hypertension played an important role because improvement of heart failure ensued when the blood pressure decreased toward normal. Davies,[51] however, found that recovery from "heart failure" (his quotes) was related to the diuresis and not to a fall in blood pressure. Gore and Saphir[52] found a high incidence of myocarditis at autopsy in patients dying from acute nephritis. However, most observers agree that the myocarditis is mild and probably does not account for the failure of the heart.

Electrocardiographic changes involving T waves are frequently seen in records of patients with acute nephritis.[53,54] However, no correlation is reported between the incidence of these changes or their degree and the symptomatology of heart failure. It seems likely that the electrocardiographic changes are related to electrolyte disturbances in or around the myocardial cells, secondary to changes in the plasma.

An interesting report on cardiac enlargement was made by Dean.[55] He found that cardiomegaly may occur with acute glomerulonephritis and persist for many years after the acute attack and after the blood pressure had returned to normal. He noted no relationship between the height of the blood pressure and cardiac size associated with either acute or chronic nephritis. The above observations suggest that heart size is not an infallible sign of heart failure in acute nephritis.

Since the technique of cardiac catheterization has become available, much has been learned about cardiac pressures and cardiac output as related to congestive heart failure and conditions simulating heart failure. Davies,[51] in England, and Eichna, Farber, Berger, Rader, Albert, and Smith,[56] in the United States, employed cardiac catheterization to measure cardiac pressures and cardiac outputs of patients with acute nephritis. They found that the pressures were elevated, but that the cardiac outputs were within normal range. Davies, as well as Eichna and his co-workers, question whether congestive heart failure actually exists in most patients with nephritis.

Eichna, Albert, and Smith[57] have shown that the signs and symptoms of congestive heart failure are related to vascular congestion and may appear when the cardiac output is normal and there is no reason to suspect heart disease. In patients treated with cortisone who did not have heart disease, these authors observed that the development of edema was associated with dyspnea, orthopnea, râles in the lungs, elevated right auricular pressures and pulmonary pressures, normal arteriovenous oxygen differences, and normal cardiac outputs. The study indicated that the signs and symptoms of congestive heart failure were related to venous and pulmonary congestion, which occur without failure of the heart. The congestion may result from an increase in tone of the blood

vessels and heart with or without an accompanying increase in local venous, pulmonary, or general systemic blood volume.

Eichna and his associates[58] studied five patients with acute nephritis who had signs and symptoms usually diagnosed as congestive heart failure. They measured cardiorenal hemodynamics and electrolyte excretions. As shown in Table IIIA, each patient with acute nephritis had an increased right auricular pressure, but the cardiac output in each was within normal limits. However, in one patient (C.) the arteriovenous differences for oxygen content were greater than normal, which indicated that the rate of blood flow to his tissues was not adequate to supply the oxygen needs of the tissues, and more oxygen had to be extracted from the available flow. This is a characteristic finding in patients with heart failure.

TABLE IIIA. RENAL AND CARDIOVASCULAR HEMODYNAMICS OF INDIVIDUAL PATIENTS WITH ACUTE GLOMERULONEPHRITIS

PATIENT	GFR	RPF	F.F.	CARDIAC OUTPUT (L./MIN.)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOL. %)	AURICULAR PRESSURE (MM./HG)
Normal	131	700	18.7	4.5–6.0	4.5–6.0	1.0–2.0
K.	41	235	18.0	4.8	5.0	7.5
P.	30	300	10.0	6.3	4.6	11.0
Hr.	70	473	15.0	5.7	5.1	7.0
Ha.	22	351	6.0	5.2	4.3	—
C.	45	215	21.0	4.3	7.2	13.0

TABLE IIIB. SUMMARY OF RENAL HEMODYNAMICS IN PATIENTS WITH RENAL DISEASE OR CONGESTIVE HEART FAILURE

	GFR	RPF	F.F.	NO. OF SUBJECTS
Normal	130	700	18.7	17
Acute nephritis	57	406	14.0	11
Congestive heart failure	68	176	38.0	5

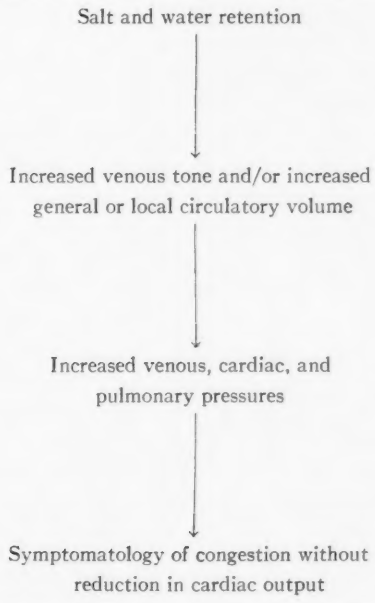
Glomerular filtration rate and renal plasma flow were reduced in all cases (Table IIIB), but instead of having the high filtration fraction characteristic of patients with heart failure, they had the low filtration fractions characteristic of patients with nephritis. The patient who had a high arteriovenous oxygen difference evidenced a filtration fraction which was nearly normal. After loss of edema it decreased. These filtration fractions may indicate that had he not had an element of congestive heart failure in association with his acute nephritis, the filtration fraction would have been low and not normal during the acute phase of his disease.

Three patients were treated with intravenous digoxin. The characteristic response of patients with congestive heart failure was not observed.[59] There

was no appreciable decrease in right auricular or venous pressure, no increase in cardiac output, and no sodium and water diuresis.

The conclusion, therefore, would be that (Table IV) the signs and symptoms usually attributed to congestive heart failure in acute nephritis are due to venous and pulmonary congestion and are associated with salt and water retention and not heart failure. However, there are some patients who probably do have heart failure at the time they have acute nephritis. Clinically, this should be determined by studying the circulation time. Patients without heart failure have a normal circulation time and those with heart failure a prolonged circulation time.

TABLE IV. PROPOSED SCHEME OF PATHOGENESIS OF VASCULAR CONGESTION IN ACUTE NEPHRITIS


Salt and water retention
Increased venous tone and/or increased general or local circulatory volume
Increased venous, cardiac, and pulmonary pressures
Symptomatology of congestion without reduction in cardiac output

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CLINICAL CORRELATIONS

The clinical and laboratory observations of patients with acute and chronic glomerulonephritis and the accompanying uremia are in general explained by the functional disorder of the kidneys. Since the kidney is one of the chief regulators of the composition of the plasma, it is not surprising to find that derangement of renal physiology is reflected quite early in changes in the plasma and extracellular fluid. The extracellular fluid is the bathing medium of the cells and its composition can alter intracellular function. Conversely, faulty cellular metabolism and permeability may also cause changes in the extracellular fluid. The concentration of substances in the extracellular fluid may, therefore, at times serve as an index of metabolic abnormalities developing in cells. However, many metabolic cellular derangements do not alter extracellular fluid

composition as it can be presently measured. The ultimate metabolic alterations in disease are due to cellular dysfunction, and, therefore, investigations of cellular functions and permeability are emphasized by many students of renal disease.

Laboratory findings of proteinuria, cylindruria, and hematuria conform with the postulate that there is increased glomerular capillary permeability in renal disease. Reduction in filtration rate readily accounts for the azotemia; glomerulotubular imbalance caused by the low filtration rate helps to explain the retention of salt, water, and subsequent appearance of edema.

The causes of arterial hypertension are not known. Although cardiac failure may occur in acute nephritis, recent data seem to indicate that in most instances there is no reduction in cardiac output in the presence of clinical signs and symptoms that are ordinarily interpreted as indicating cardiac failure. Electrocardiographic changes, gallop rhythm, enlargement of the heart, and hypertension are not necessarily evidence of heart failure in acute nephritis. In the terminal stages of chronic nephritis, heart failure does occur and is probably secondary to hypertension.

As the disease progresses to the chronic stages, further reduction in filtration rate, tubular dysfunction, and increased glomerulotubular imbalance contribute to the observed changes. The accumulation of sulfate and phosphates is related to the reduction in filtration rate. The decreased ammonia formation is probably due to tubular disease. Impairments of the latter function lead to the metabolic acidosis of chronic nephritis.

Disturbances in serum electrolyte concentration are common in acute and chronic nephritis. As previously stated, sodium may be lost by the kidneys with consequent hyponatremia. Potassium may be retained as a result of renal insufficiency. Cellular breakdown and defects in the cellular uptake of potassium probably contribute to the hyperkalemia. Hypokalemia due to renal loss is occasionally seen. Changes in serum concentration do not always reflect cellular changes, nor do these changes reveal whether losses from, or excesses of, electrolytes in the body occur. Thus, a normal or high plasma potassium concentration can exist at the same time as cellular excess or deficiency.[61] Similarly, a low serum sodium level may not indicate body loss of sodium; it can occur if the extracellular fluid is diluted or if sodium enters cells, bone, or other tissues. The only possible way to determine the etiology of the disturbances is to follow the daily excretion of electrolytes, using urinary electrolyte concentration and daily volume determinations. The daily intake and output can then be used to indicate whether losses or excesses have occurred, and rational therapy may then be instituted.

The accompanying table of renal function tests (Table V) attempts to indicate the counterparts of the specific measurements of renal functions used in clinical medicine. The most readily available clinical test of filtration rate is endogenous creatinine clearance. The test is simple and yields reliable clinical data, although the methods for analysis are not entirely specific and discrepancies do occur. Phenolsulfonphthalein (PSP) is excreted rapidly by the renal tubules. Its excretion after intravenous administration is probably a reflection of renal

TABLE V. TESTS FOR RENAL FUNCTION*

FUNCTION	RENAL FUNCTION TESTS SPECIFIC MEASUREMENTS	CLINICAL TESTS
Glomerular filtration	Inulin clearance	Creatinine clearance Urea clearance Plasma urea concentration
Renal plasma flow	PAH clearance	PSP excretion
Proximal tubular mass	Excretory T_{mPAH} Reabsorptive T_mG_{lucose}	PSP excretion
Distal tubule	Electrolyte balance Acid-base balance Ammonia formation	
Collecting ducts	Tc mH_2O	Specific gravity

*Modified from table by Earle.[60]

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plasma flow, provided tubular function is not greatly impaired. When kidney damage is severe, the PSP excretion test is more a measure of tubular excretory mass.

Physiologic investigations have helped considerably in understanding the disturbances of discrete renal function in nephritis. Much has been learned and more will be disclosed as a result of constant interchange of knowledge obtained at the bedside, in follow-up in outpatient departments, and in the clinical and investigational laboratories.

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THE NEPHROTIC SYNDROME*

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IT IS indicated in the introductory statement to this symposium that disagreement persists concerning the position of the nephrotic syndrome in the general classification of kidney disease. However the question implied by this statement will be answered eventually; it seems clear that the following clinical observations must be taken into account[1]:

1. The nephrotic syndrome is characterized by intermittent edema associated with considerable proteinuria, with low concentrations of certain plasma proteins, especially albumin and gamma globulin, and with hyperlipemia.

2. It may or may not be accompanied by nephritic manifestations (reduced kidney function, hematuria, hypertension).

3. It may appear in the absence of any evidence of previous kidney disease or during the course of classical diffuse glomerulonephritis.

4. It may appear in association with certain recognized systemic diseases not primary in the kidney.[2,3]

5. It may occur during the administration of certain drugs (Tridione,[4] gold salts[5]) or following bee stings or exposure to poison oak.[6]

6. It is usually not preceded by evidence of systemic infections (Group A hemolytic streptococci or others).

7. It may result in complete recovery or in death from renal insufficiency.[7]

From these clinical observations, it seems probable that a variety of insults may cause the type of glomerular damage which results in the occurrence of the nephrotic syndrome. However, in most instances the syndrome appears in the absence of any recognizable associated disease or exposure to toxic agents; and it is in this group of patients that the greatest disagreement concerning classification exists. Until more is known about etiology, it seems unlikely that this problem will be solved. Thus far, it has been clarified very little for the clinician by the extensive investigations of the pathology of the kidney (examination of

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tissue obtained either at autopsy or more recently by renal biopsy[8,9]), of the biochemical and physiologic alterations,[1] or of the experimental kidney disease[10] which resembles the nephrotic syndrome in man.

Among clinicians, the greatest divergence in views concerning this group of patients with the nephrotic syndrome has been between those who consider it to be a distinct disease entity and those who believe that it represents a phase of diffuse glomerulonephritis, even when it occurs without evidence of previous kidney disease. That pediatricians, for the most part, have subscribed to the former belief is understandable from a consideration of certain characteristics of the disease in children. For example, pediatricians[7] have observed the disease most frequently in children who are under 5 years of age and who rarely have evidence of previous kidney disease (classical glomerulonephritis is uncommon before 5 years of age). Only about one-half of the children show nephritic manifestations at the onset; and rarely, if ever, are they found to have associated nonrenal systemic diseases. Of greatest importance, perhaps, is the fact that approximately one-half of children with the nephrotic syndrome recover. These clinical experiences, taken together with the observation that children with classical acute glomerulonephritis rarely, if ever, develop the nephrotic syndrome, have led most pediatricians to consider the nephrotic syndrome as a specific disease distinct from classical glomerulonephritis.*

In contrast to this interpretation, many internists hold the view that in the absence of associated nonrenal systemic diseases the nephrotic syndrome in adults represents a phase of diffuse glomerulonephritis, even when it occurs without evidence of previous kidney disease. In considering the source of these divergent views, the most important clinical fact would appear to be that recovery of a child with the nephrotic syndrome occurs frequently, whereas recovery is rare in adults. If it is accepted that the difference in mortality rate between children and adults with the nephrotic syndrome is of major importance, then the crucial question becomes whether this difference in the final outcome is due to differences in response to the same disease occurring at different ages or to the existence of two diseases. The answer to this question is not at hand. However, a preliminary analysis of the course of the nephrotic syndrome in the series of patients observed at the hospital of the Rockefeller Institute has bearing on this question.† The mortality rate in these patients is shown in Table I in relation to the age of the patients at the time of onset of the disease.

The relatively small number of patients in some of the age groups in this series, particularly in the groups over 30 years, precludes firm conclusions concerning the relationship between mortality rate and age of the patient at the onset of the nephrotic syndrome. However, to our knowledge no similar data are

*At the present time, most pediatricians do not consider it useful to separate children with the nephrotic syndrome into two groups depending upon the presence or absence of nephritic manifestations (pure or lipoid nephrosis versus mixed nephritis). In the recent literature, the terms nephrosis and nephrotic syndrome have been used interchangeably by most writers to include children with and without nephritic manifestations.

†Observations on these patients were made over a period of thirty years in the clinic of Dr. D. D. Van Slyke at the Hospital of the Rockefeller Institute. The patients were studied carefully during the period prior to the introduction of effective antimicrobial agents and corticosteroids. A detailed analysis of these data by Van Slyke and Eder is in preparation.

TABLE I. RELATIONSHIP BETWEEN THE AGE OF PATIENTS* AT THE ONSET OF THE NEPHROTIC SYNDROME AND THE MORTALITY RATES (DATA FROM THE HOSPITAL OF THE ROCKEFELLER INSTITUTE)

AGE (YEARS)	NUMBER OF PATIENTS	UNCORRECTED* MORTALITY (PER CENT)	CORRECTED MORTALITY† (PER CENT)
0 — 4	43	58	42
5 — 9	17	65	41
10 — 14	18	78	56
15 — 19	24	71	67
20 — 24	12	50	50
25 — 29	18	67	61
30 — 34	8		
35 — 39	4		
40 — 44 (30 and older)	4 (22)	91	86
45 — 49 (30 and older)	3		
50 — 54 (30 and older)	1		
55 — 60 (30 and older)	2		

*Patients with systemic diseases not primary in the kidney were excluded in this series.

†Excluding patients who die of causes other than renal insufficiency. Infections were the major cause of such deaths in the younger age groups.

available from other sources. The results in this series suggest that there is no abrupt change in the mortality rate from childhood to adulthood. These data would support the suggestion that the nephrotic syndrome may represent the same disease in children and in adults.

Our present view, therefore, concerning the position of the nephrotic syndrome in the general classification of kidney disease continues to be based almost entirely on clinical observations. Such observations suggest that the nephrotic syndrome may occur as a phase of classical glomerulonephritis, just as it may occur as part of certain systemic diseases not primary in the kidney. However, there is compelling clinical evidence to support the belief that in children the nephrotic syndrome may, and almost always does, occur as a disease of unknown etiology but distinct from the glomerulonephritis associated with infection by the hemolytic streptococcus. The data presented on the relationship between mortality rates and the age of patients at the onset of the nephrotic syndrome suggest that, in adults as well as in children, the nephrotic syndrome may represent, in the absence of associated systemic disease, a disease distinct from glomerulonephritis. If accepted, this suggestion should have profound influence on attitudes toward treatment and prognosis of the nephrotic syndrome in adults. The favorable results observed recently in the treatment of adults with adrenocortical steroids[11,12] (see section below on Treatment) would appear to add further support to this suggestion.

PHYSIOLOGIC ASPECTS OF THE NEPHROTIC SYNDROME

In the nephrotic syndrome there are marked alterations in the metabolism of (1) protein, (2) lipids, and (3) salt and water. It is our opinion that the chain of events leading to these alterations is a consequence of an initial glomerular lesion.

Protein Metabolism.—The initial alteration in protein metabolism in patients with the nephrotic syndrome is the appearance of marked proteinuria. It has been shown that the primary cause of this proteinuria is an alteration in the glomerular membrane which permits large amounts of protein to pass into the glomerular fluid.[13] The role of tubular reabsorption of protein in determining the final quantity of protein appearing in the urine is as yet undetermined. Some have suggested that, in the presence of high concentrations of protein in the glomerular fluid, the absolute rate of tubular reabsorption of protein may be increased.[13] Others have suggested that decreased reabsorption of this large quantity of protein may contribute significantly to the quantity of protein in the urine. The latter concept is derived from data on the renal clearance of hemoglobin[14] which have been interpreted as demonstrating the existence of a maximal rate of tubular reabsorption (Tm) of this protein. The data of Chinard and his associates[13] obtained by infusing concentrated human serum albumin into patients with the nephrotic syndrome show no evidence of a Tm for albumin, since the albumin clearance remained constant over a fairly wide range of concentrations of albumin in plasma. These authors did note that immediately following large infusions of albumin, the albumin clearance increased. They interpreted this increase as being due to alterations in the glomerular wall. Hardwicke and Squire[15] have recently presented data suggesting that there is a Tm for protein in patients with the nephrotic syndrome, but it should be noted that they used data obtained immediately following infusions of albumin (when according to Chinard, and his associates, marked alterations in the glomerular walls would occur) and that their patients had higher levels of plasma albumin.

Three other explanations have been offered as to the cause of proteinuria: (1) The increased passage of proteins through the glomerular wall is due to the presence of an abnormal type of albumin in patients with the nephrotic syndrome. Although some support for this view is offered by the differing rates of diffusion of urine and plasma albumin,[16] the evidence from immunochemical methods[17] and isotopic labeling[18] does not support this thesis. (2) There is no abnormality in the glomerular wall but there is incomplete reabsorption of proteins normally appearing in the glomerular fluid in concentrations of 20 to 30 mg. per 100 ml.[19] The evidence of Chinard and his associates disproves this hypothesis. (3) The renal tubules secrete the protein into the urine. There is no evidence to support this theory. It is very unlikely in view of the presence of protein coagula in Bowman's space. In addition, there are interesting experiments[20,21] with aglomerular fish and amphibians with double blood supply to the kidney which indicate that a functioning glomerulus is necessary for proteinuria to occur.

Thus far, attention has been devoted primarily to the excretion of albumin, but other plasma proteins also appear in the urine of patients with the nephrotic syndrome. Using electrophoretic methods for determining protein concentrations, Hardwicke and Squire found that on the average the clearance of alpha$_1$ globulins were 124 per cent of those of albumin, while the clearances of alpha$_2$, beta, and gamma globulin were 13, 29, and 27 per cent, respectively, of the albumin clearances. These authors properly emphasized that clearances in which globulins are measured by electrophoretic methods have limited meaning because of the heterogeneity of the globulins of various electrophoretic mobilities.

Using immunochemical methods, Gitlin, Janeway, and Farr[22] found gamma globulin clearances approximately the same as those of Hardwicke and Squire. However, the clearance of the iron-binding beta globulin was 65 per cent of the albumin clearance.

As might be anticipated from the studies of protein excretion, the most striking alteration in the plasma proteins is decreased concentration of plasma albumin. The alpha$_1$ globulins tend to be normal or slightly decreased; the beta globulins are increased, in part because of the increase in beta lipoproteins in this fraction; gamma globulins are markedly decreased.

It is generally accepted that the hypoproteinemia in patients with the nephrotic syndrome results from the massive proteinuria. Nevertheless, the problem of protein synthesis in the nephrotic syndrome is of considerable interest. It has been apparent to clinicians that patients with similar amounts of proteinuria but with different plasma protein concentrations must differ either in their rate of protein synthesis or catabolism. This problem has been studied recently by Gitlin, Janeway, and Farr, using I^{131} labeled plasma proteins. They found that the disappearance rate of injected albumin was markedly increased in patients with the nephrotic syndrome. A part of this increase was accounted for by urinary excretion, but it was concluded that there was also an increase in the rate of catabolism of albumin. However, the total albumin pool was decreased so that the absolute rate of catabolism (grams per day) was near normal levels. The absolute rate of albumin synthesis, the sum of catabolism plus urinary excretion, was calculated by Gitlin and associates to be at the upper limits of normal. They obtained very similar results using labeled gamma globulin and iron-binding protein. From these studies, we would conclude that the primary cause of hypoproteinemia in patients with the nephrotic syndrome is urinary excretion of protein rather than a decrease in the rate of protein synthesis which appears to be normal or even slightly above normal.

Lipid Metabolism.—Patients with the nephrotic syndrome exhibit marked hyperlipemia. In addition to the elevation in serum cholesterol, which is well known, there are proportional increases in the concentrations of phospholipids and even more marked increases in the concentrations of triglycerides.[23] All of the serum lipids exist in association with proteins as lipoproteins. In the nephrotic syndrome these increased lipid concentrations are reflected in markedly increased concentrations of the low density lipoproteins. By ultracentrifugation the concentration of the lipoproteins of high triglyceride content (density less than 1.019; S_f 12-400) are markedly increased.[24] By electrophoresis these proteins appear as beta$_1$ lipoproteins[25]* and are obtained by Cohn fractionation in fraction I + III.[26] The high density or alpha lipoproteins are present in normal or slightly reduced concentrations. The lipoproteins present in increased concentrations in patients with the nephrotic syndrome are qualitatively no different from those found in normal subjects.[24]

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*Since this manuscript was submitted, Kunkel and Trautman (Kunkel, H. G., and Trautman, R.: The Alpha$_2$ Lipoprotein of Human Serum. Correlation of Ultracentrifugal and Electrophoretic Properties, J. Clin. Invest. **35**:641, 1956) have shown that these low density lipoproteins have the mobility of γ_2 globulins.

The cause of these increased lipoprotein concentrations is not known. It must be recognized that this is a complex problem involving synthesis, degradation, and mobilization of a variety of substances including cholesterol, phospholips triglycerides, and proteins. Thus, an alteration in cholesterol metabolism may be entirely secondary to an alteration in the metabolism of other constituents of the lipoproteins. For example, Gitlin and Cornwell[27] have recently demonstrated a reduced rate of turnover of the low density beta lipoproteins (S_f 15-400) in patients with the nephrotic syndrome. The rate of disappearance of labeled serum cholesterol has been studied by several groups. London, Sabella, and Yamasaki,[28] using deuterium, found a decrease in the turnover time of serum cholesterol, whereas Hellman and his associates,[29] measuring carbon-labeled cholesterol, found that turnover time did not differ from normal. Such discrepant results could be due to differences in their patients, in whom the concentration of serum cholesterol could have been rising, declining, or constant. Moser and Emerson[30] observed a decreased rate of turnover of phospholipid in patients with the nephrotic syndrome. In general, these data suggest that the hyperlipoproteinemia may be a consequence of decreased removal of lipoproteins from the plasma.

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Studies on animals with experimental nephrosis are in accord with this hypothesis. Marsh and Drabkin[31] demonstrated that liver slices from nephrotic animals incorporated labeled acetate into cholesterol at a lower rate than did normal rats. They showed further that there was a redistribution of cholesterol in nephrotic rats with the total body cholesterol remaining constant but more of it appearing in the blood, kidney, and liver and less in the other organs. Recent studies of Rosenman, Byers, and Friedman[32] relate the hyperlipemia to the glomerular lesion and the consequent loss of albumin. They demonstrated that, if the loss of albumin was prevented in rats with experimental nephrosis either by performing a unilateral nephrectomy and anastomosing the ureter of the remaining kidney to the vena cava or by constant albumin infusion, hyperlipemia did not occur. This correlation between concentrations of serum albumin and hyperlipemia is evident in clinical studies.

Salt and Water Metabolism.—The most prominent sign of the nephrotic syndrome is edema. The accumulation of edema is the consequence of renal tubular reabsorption of filtered sodium, chloride, and water in excess of that required to maintain a normal extracellular fluid volume. The mechanism of this excess retention has been the subject of considerable investigation not only in patients with the nephrotic syndrome but in other edematous states such as congestive heart failure and hepatic cirrhosis. The increased tubular reabsorption could be due to a reduction in the rate of glomerular filtration (GFR) relative to tubular reabsorption or an increase in tubular reabsorption relative to GFR. The reduction in GFR may occur directly as the result of glomerular lesions or it may be a hemodynamic phenomenon. Evidence for the latter has been obtained in the studies of Eder and his associates,[33] who found that in the nephrotic syndrome there was a reduction in plasma volume with associated circulatory inadequacy manifested clinically in occasional patients by mild vertigo, feelings of faintness, palpitation, and thirst; it was also manifested

by a decrease in renal blood flow with a decrease in GFR. When the plasma volume increased spontaneously or following the administration of concentrated human plasma albumin, the GFR frequently rose. This increase in GFR was accompanied by increased excretion of sodium, chloride, and water. In certain patients treated with adrenocorticotrophins or adrenal steroids, the GFR rose without measurable increases in plasma volume. In these instances the increase in GFR could be due to a direct effect of the hormones on the glomerular lesions.

In other patients, increased salt and water excretion was not accompanied by changes in GFR, suggesting that primary tubular factors may also be operative. Two major possibilities have been considered: (1) that tubular preponderance is a consequence of increased stimulation of the tubular system responsible for water reabsorption and under the control of antidiuretic hormone (ADH); (2) that tubular preponderance is a consequence of increased stimulation of the tubular system responsible for sodium and chloride reabsorption and under the control of the adrenocortical hormones. The former possibility has been reviewed recently[1] with the conclusion that, at the present time, there is no clear-cut evidence that antidiuretic substances play a role in the production of nephrotic edema. Of interest in regard to this question is the recent observation that a hypertonic urine can be produced in experimental animals merely by reducing the GFR independently of ADH effects.[34]

The second possibility, increased tubular reabsorption of sodium and chloride due to increased activity of adrenocorticosteroids, has been the subject of extensive investigations by Luetscher and his associates and has been reviewed recently in this JOURNAL.[35] It has been shown that in patients with the nephrotic syndrome, the urine contains abnormally large amounts of a salt-retaining material which has been identified as aldosterone.[36] When diuresis occurs either spontaneously or due to administration of concentrated human plasma albumin, adrenocortical steroids, or corticotrophin, the urinary excretion of aldosterone decreases. The interpretation of these data is as yet uncertain. It may be that the primary mechanism for salt retention in the nephrotic syndrome is increased aldosterone activity. However, it is also possible that the increased excretion of aldosterone is a secondary mechanism superimposed on a primary decrease in GFR.

NATURAL HISTORY OF THE NEPHROTIC SYNDROME

The gradual appearance of edema in a child or adult who in most instances has been in good health and who is found to have considerable proteinuria, low serum albumin, and high serum cholesterol concentrations establishes the diagnosis of the nephrotic syndrome. During the active stage of the disease in an untreated patient, edema of varying degrees of severity may be constant or intermittent and may be associated with anorexia, fatigue, diarrhea, and vomiting, and a variety of alterations in behavior and attitudes. During periods of edema, untreated children with the nephrotic syndrome have a markedly increased incidence of severe bacterial infections. This feature of the disease, which is almost universal among young children, is much less prominent in older children and young adults and strikingly absent in older adults.

Duration of Disease.—The duration of the nephrotic syndrome in 124 of the patients observed at the Hospital of the Rockefeller Institute is shown in Table II. Recovery* occurred in 44 of this group of 124 patients (representing for the most part, but not precisely, the same group of patients included in Table I). Among the 44 patients who *recovered*, the median values for the duration of the disease in the various age groups ranged from 22 to 57 months with extreme values of 4 and 156 months. Although the highest median value was observed in the patients 30 years of age or older, there were only 4 patients in this group. In the groups of patients whose disease began before 30 years of age, there does not appear to be any consistent relationship between the age of the patient at the onset of the disease and the duration of the disease in patients who recover.

TABLE II. DURATION OF THE NEPHROTIC SYNDROME IN RELATION TO AGE OF PATIENTS AT THE ONSET AND TO THE FINAL OUTCOME (DATA FROM THE HOSPITAL OF THE ROCKEFELLER INSTITUTE)

AGE (YEARS)	PATIENTS WHO RECOVERED			PATIENTS WHO DIED OF RENAL INSUFFICIENCY		
	NUMBER	MONTHS FROM ONSET TO RECOVERY		NUMBER	MONTHS FROM ONSET TO DEATH	
		MEDIAN	RANGE		MEDIAN	RANGE
0 — 4	18	43	(4–106)	13	29	(2–81)
5 — 9	5	35	(8–64)	6	61	(14–120)
10 — 14	5	41	(30–83)	10	46	(4–57)
15 — 19	5	22	(11–80)	17	46	(22–120)
20 — 24	3	41	(35–156)	5	35	(30–192)
25 — 30	4	32	(17–72)	6	82	(38–102)
30 and older	4	57	(14–97)	23	44	(3–192)
Total	44			80		

Among the 80 patients who died, the median values for the duration of the disease in the various age groups ranged from 29 to 82 months with extreme individual values of 2 and 192 months. Although the range of individual and median values is very great, it would appear that the duration of the disease among patients who die is shorter in the children under 5 years of age. In this group, the majority of the patients died during the active stage of edema. A smaller proportion of the young children survive the active stage but emerge from it with persistent loss of kidney function. Although these patients may live for a few years in apparently good health, death from renal insufficiency ultimately occurs. In older children and particularly in adults, the latter course is observed more frequently and may last for many years. However, deaths during the active stage also occur in these patients.

*Patients in this series were considered to have recovered only when, in addition to being free of symptoms, their values for urea clearances, plasma albumin, and total protein concentrations and rates of urinary excretion of protein and red blood cells were all within normal limits for a minimum period of six months.

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Prognosis.—It is apparent from Table I that the age of the patient at the onset of the disease is a valuable prognostic factor. However, the more important question in patients of any age is whether or not the course of the disease can be predicted in an individual patient. Although such a prediction cannot be made with certainty from clearance data, we believe it is of value to know the status of kidney function in an individual patient with nephrosis, and clinically we believe the clearance of urea serves this purpose.[37] If the urea clearance is normal we believe we can say that the patient can recover; if the clearance is decreased we can say that, in order for the patient to recover, the clearance will have to return to normal, which it may do. It is only when the clearance is markedly reduced over a long period of time that we can say that recovery cannot be expected.

It was thought formerly that the presence or absence of nephritic manifestations provided a means of predicting the outcome, particularly in children with the nephrotic syndrome. However, careful investigation of this problem has failed to confirm this supposition. For example, in a series reported recently,[7] 11 of 28 children who had apparently recovered from the nephrotic syndrome had shown nephritic manifestations at the time of the first examination. The fact that 11 of 15 children who had died had shown such manifestations at the onset indicates a significant difference in the incidence of recovery between the two groups. However, such data do not permit the physician to say, in talking with the parents of a child with the nephrotic syndrome, that an individual child will die or recover on the basis of the presence or absence of evidences of nephritic manifestations at the onset of the disease.

TREATMENT

The treatment of patients with the nephrotic syndrome may be considered in terms of general measures, treatment of edema, and the use of agents which may have an effect on the underlying kidney disease.

The *general measures* are diet, physical activity, and the management of infections.

Diet.—In the absence of renal insufficiency, little if any change in the diet is suggested. A diet high in protein has been considered of value in the past, and recently Blainey[38] has re-emphasized this point of view. However, the observations of Farr[39] and the consistent resistence of most children in the active stage to such diets lead us to believe that it is more reasonable to offer a diet with a protein content appropriate to the age and weight of the patient. Moderate salt restriction is suggested on the basis that during periods of edema the amount of salt taken may have an effect on the amount of edema.

Activity.—It seems reasonable to avoid exhausting physical activity in a patient with the nephrotic syndrome. However, in children we do not recommend restriction of ordinary activity beyond that which the patient might impose upon himself during periods of massive edema. In certain adults, however, the extent of edema may be favorably affected by a period of bed rest.

Infections.—It is our present opinion that during the active stage of the disease children with the nephrotic syndrome should receive continuous pro-

phylactic antibiotics. For this purpose we have given to children 300,000 units of penicillin (Bicillin) by injection once a day, or 200,000 unit tablets twice a day, alternating at monthly intervals with oral oxytetracycline (Terramycin) (5 mg. per kilogram two times per day). In adults, infections are not a sufficient problem to warrant prophylactic therapy with antibiotics.

During periods of edema, the child with the nephrotic syndrome is very susceptible to severe generalized infections. Peritonitis, which may be accompanied by septicemia and cellulitis, is the most common of these severe infections. The presence of ascites may mask the classic sign and symptoms of peritonitis and it must be suspected, therefore, whenever a child with nephrosis develops a fever and looks sick. The fact that these infections were the cause of death in over 50 per cent of children with the nephrotic syndrome before effective antimicrobial drugs were available emphasizes the importance of early diagnosis and vigorous treatment. Whereas in the past the pneumococcus caused most of these infections, at present they are due more frequently to other organisms, probably most often to *Escherichia coli*. An attempt should be made to determine the organism from blood and ascitic fluid cultures, but treatment should be started promptly with large doses of antimicrobial therapy designed to provide the broadest possible coverage.

Treatment of Edema.—Of the many agents or procedures which have been suggested for relieving edema in patients with the nephrotic syndrome, the only one which we use specifically for this purpose at present is abdominal paracentesis. Ordinarily, we do not advise the use of dextran, salt-poor albumin, osmotic diuretics, mercurial diuretics, ion exchange resins, very low salt diets, antihistamines, or thyroid extract.

Specific Treatment (?).—It has been established that several agents (corticotrophin or adrenocortical steroids,[40,41] nitrogen mustards,[42] thiosemicarbazone,[43] measles virus,[44] and malaria[45]) are capable of inducing in edematous patients with the nephrotic syndrome the same type of profuse, sustained, complete diuresis which may occur spontaneously or occasionally following severe infections. In addition, such diureses may be accompanied by striking improvement in certain physiologic and biochemical characteristics of the disease (decreases in hyperlipemia and rate of urinary excretion of protein and aldosterone; increases in serum albumin and glomerular filtration rate).[1,7]

It seems clear that prolonged adminstration of corticotrophin[46,47] or adrenocortical hormones[48,49] *after* a diuresis has been induced may in many instances prevent the recurrence of edema.

The crucial question at present is whether such regimens of prolonged therapy favorably influence the final outcome of the disease. From an analysis of the course of the disease in 779 children observed in 18 clinics throughout the country, Riley and Fertig[50] have concluded recently that "prolonged and intensive use of adrenocortical-active hormone therapy in childhood nephrosis not only improves the clinical status but also extends life." In very much smaller series of adults with the nephrotic syndrome, Baxter, Goodman, and Orloff[11] and Merrill[12] have observed complete remissions in about one-fourth of their patients after steroid therapy and improvement in about two-thirds. Although these and other

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reports leave unanswered the question of the effect of such treatment on the final outcome, such analyses provide the basis for our present attitude toward the use of these hormones in patients with the nephrotic syndrome, as follows:

We suggest that therapy with hormones be started as soon as the diagnosis of the nephrotic syndrome is established. At present, we recommend that prednisone be given in the following dosages: children under 5 years of age, 40 mg. per day; children over 5 years of age and adults, 60 mg. per day. It should be emphasized that this choice of hormone and the dosages recommended are arbitrary. There is no conclusive evidence that prednisone is superior to cortisone, hydrocortisone, or corticotrophin. Although dosages of prednisone as high as 125 mg. per day have been used successfully in adults,[12] the data of Baxter, Goodman, and Orloff[11] suggest that dosages as low as 40 mg. per day are adequate. The daily dosage is given in four equal doses distributed as equally as practicable throughout the twenty-four hours. The dosage is continued for varying periods of time depending upon the response of the patient. If a complete diuresis occurs within fourteen days, continuous daily therapy is discontinued after this period and the patient is started on a similar dosage intermittently (40 or 60 mg. per day given three days of each week). If no diuresis has occurred by fourteen days, the dosage is continued daily until a diuresis occurs, after which it is given intermittently. If no diuresis has occurred by the twenty-eighth day, the hormone is discontinued and *no* intermittent therapy is given. In the latter instance, we suggest observing the patient for one to two months and, if edema persists, trying the same regimen again.

We give therapeutic doses of antimicrobial therapy designed to provide the broadest possible coverage to children receiving steroids continuously. Antibiotics are given in prophylactic doses during the period of intermittent therapy. During steroid treatment, we advise a regular diet with only moderate salt restriction and the addition of potassium in a dosage of about 3 meq. per kilogram per day only if the patient is eating poorly. It is important in preventing complications that the patient be examined frequently by the physician with especial attention to the blood pressure and to evidence of infection. Whether or not adequate observation requires hospitalization during the periods of continuous treatment will depend upon the circumstance. The tendency of cortisone to decrease the rates of statural growth and of skeletal maturation, as reported by Sobel[51] and by Blodgett and associates,[52] has been observed in children with the nephrotic syndrome. However, the compensatory growth spurt which is reported to occur when the hormone is discontinued suggests that the child's ultimate stature will not be altered.

The important question of how long intermittent therapy should be continued is unsettled. In agreement with others,[53] we believe that measurement of the rate of protein excretion provides the most useful guide for determining the duration of therapy. At present, we recommend giving intermittent therapy for one or two months after the rate of protein excretion has fallen to below 100 mg. per 12 hours. If, in the absence of other evidences of activity, proteinuria persists despite intermittent therapy, we usually discontinue therapy after about six months and start again only if proteinuria increases. If a true exacerbation

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occurs while the patient is on intermittent therapy, daily steroid therapy may be resumed either immediately or after a period of one or two months during which no therapy is given.

SUMMARY

The nephrotic syndrome is characterized by intermittent edema associated with considerable proteinuria, with low concentrations of certain plasma proteins, especially albumin and gamma globulin, and with hyperlipemia. The nephrotic syndrome may occur as a phase of classical glomerulonephritis or as part of certain systemic diseases not primary in the kidney. However, there is compelling evidence to support the belief that in children the nephrotic syndrome may, and almost always does, occur as a disease of unknown etiology but distinct from the glomerulonephritis associated with infection by the hemolytic streptococcus. The fact that the mortality rate does not change abruptly from childhood to adulthood suggests that apart from those few cases occurring as a stage of glomerulonephritis or as a part of certain systemic diseases, the nephrotic syndrome represents the same disease in adults as in children.

Proteinuria in patients with the nephrotic syndrome is attributed to an alteration in the glomerular membrane which permits large amounts of protein to pass into the glomerular fluid, and the primary cause of hypoproteinemia is ascribed to urinary excretion of protein.

In patients with the nephrotic syndrome, the concentration in serum of the low density beta lipoproteins rich in triglycerides, cholesterol, and phospholipids is usually increased. The cause of these alterations is not known, but recent evidence suggests that they may be related to the urinary loss of plasma albumin.

Edema in patients with the nephrotic syndrome is due to renal tubular reabsorption of filtered sodium chloride and water in excess of that required to maintain a normal volume of extracellular fluid. The question of whether the primary alteration is a reduction in glomerular filtration rate or an increase in tubular reabsorption has not been resolved.

A review of the course of patients with the nephrotic syndrome emphasizes the chronic nature of the disease. The median time from onset to recovery varied from 22 to 57 months in different age groups, with great variability within groups. In the group of patients who died, the median time from onset to death ranged from 29 to 82 months. The corrected mortality was slightly over 40 per cent in the group of patients under 10 years of age and increased with age to 86 per cent in patients over 30 years of age.

Although general measures in treatment are of great practical importance, of greater significance at the present time are the problems concerning the use of corticotropin or adrenocortical steroids. Present evidence suggests that these agents should be used to induce diuresis and that they should be given for a prolonged period thereafter.

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THERAPY OF ACUTE AND CHRONIC GLOMERULONEPHRITIS

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IT IS reasonable to assume that an unknown number of patients who have acute glomerulonephritis or an exacerbation in the course of chronic glomerulonephritis remain asymptomatic. Transient mild symptoms which may appear often are attributed by the patient to an antecedent infection, fatigue, or similar nonspecific events. Such patients are not seen by a physician and the illness or the acute phase resolves without therapy. On the other hand, the development of edema, the appearance of hematuria or other urinary symptoms, the onset of headaches, of visual disturbances, or of respiratory distress may lead to a visit to the physician. Though it is reasonable to assume that the illness is more severe and the prognosis for resolution less favorable in such patients, there are no comparative figures to support such a conclusion. However, even the mildest initial attack or exacerbation deserves serious attention in view of the risk of permanent renal damage. Therefore, in each such patient the physician must make short- and long-term decisions concerning limitation of physical activity, the use of antibiotics and of adrenocortical steroids, and the prescription of diet and fluid intake in addition to the more immediate therapy of any manifestations such as edema, hypertension, gastrointestinal symptoms, congestive heart failure, anemia, or convulsions. The advent of far-advanced renal failure in acute glomerulonephritis, during an exacerbation of pre-existent nephritis or as a terminal phase of chronic glomerulonephritis, greatly complicates such therapy.

GENERAL PRINCIPLES OF THERAPY OF ACUTE GLOMERULONEPHRITIS OR OF ACUTE EXACERBATIONS SUPERIMPOSED ON CHRONIC GLOMERULONEPHRITIS

Particular care must be taken in acute or chronic glomerulonephritis to avoid regimens which may upset equilibria that have enabled the patient to function effectively despite the presence of renal disease or renal failure. Principles of such therapy are summarized in Table I and presented in detail in the sections which follow.

Limitation of Physical Activity.—It is customary to place such patients at bed rest since hypertension is thereby reduced, blood pressure fluctuations are minimized, and urinary abnormalities tend to decrease.[1a-l] However, it is well to recall that, save for the demonstration by Akerren and Lindgren[1m,n]

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TABLE I. THERAPY OF ACUTE GLOMERULONEPHRITIS OR EXACERBATION OF COMPENSATED CHRONIC GLOMERULONEPHRITIS

BED REST	H_2O	CHO	FAT	PROTEINS	Hg^{++} OR OTHER DIURETICS	VOMITING, CONGESTIVE HEART FAILURE, HYPERTENSION, CONVULSIONS, ANEMIA	ANTIBIOTICS	STEROIDS
Until edema and hypertension have cleared, or about one month; limited activity thereafter	*ad lib* with enough for urine volume and insensible loss unless anurie (see Table II)	*ad lib* with minimum of 100 Gm. q.d.	*ab lib*	? Restrict to 0.5 Gm. q.d.; Restrict if anuric (see Table II)	No	See Table IV	Penicillin (see text for dosage) for residual infections; prophylactically and especially with any new infections in an active glomerulonephritis. Sulfonamides and other antibiotics with renal toxicity to be avoided	May be useful in adequate pharmacologic dosage: 300 mg. cortisone orally or 200 mg. ACTH intramuscularly daily for four weeks while on 50 mg. sodium diet; 1 Gm. KCl t.i.d. unless serum potassium elevated, USP hexavitamin, and ferrous sulfate

that early ambulation of 57 juvenile acute glomerulonephritics had no adverse effect on convalescence or recovery, the value of routine immobilization has not been critically examined. In view of the uncertainty as to optimal policy and especially since restlessness in bed can in itself be looked upon as physical exertion, it is our custom to enforce bed rest during the phase of edema, hypertension, or congestive failure only, i.e., usually up to the fourth week, and to limit physical activity during the remainder of the convalescence without continuous confinement to bed.

Use of Antibiotics and of Adrenocortical Steroids.—Before turning to the principles of diet, fluid, and electrolyte therapy during the acute phases of glomerulonephritis, the possible benefits of antibiotic or of adrenocortical steroid prescriptions will be discussed.

Penicillin and other antibiotic therapy: It is recognized that the antecedent infection, often due to a Group A type 12 hemolytic streptococcus,[2a-e] may be over by the time acute glomerulonephritis appears. However, there is a place for antibiotic therapy in the acute phase or in exacerbations of glomerulonephritis. Thus, if there is evidence of a residual β-hemolytic streptococcal or other bacterial infection, or if nasopharyngeal or other cultures are positive for pathogens, the patient should receive either a single injection of 1,200,000 units of benzathine penicillin intramuscularly, or 400,000 units of oral penicillin or 200,000 units of intramuscular penicillin, each day for ten days.[3a-d] Sulfonamides probably should not be used because of their sensitizing properties.[3e-f] Any coincidental or chronic infection should also be treated. The urinary tract should be particularly examined in this regard, though traditionally the clinicians have paid more attention to the tonsils, teeth, and sinuses. Finally, the occurrence of any respiratory infection during the course of glomerulonephritis should serve as a signal for antibiotic therapy. However, it should be kept in mind that, once healed, glomerulonephritis and rheumatic fever differ in this regard. The former does not tend to recur[4a-c] and presumably does not require prophylactic antibiotics.

It has also been suggested that antihistaminics might be of benefit in the therapy of acute nephritis, but reported experience with these agents is limited.[4d,e]

Treatment with ACTH, cortisone, or related agents: The authors[5a-d] and other workers[5e-g] have been impressed with the efficacy of ACTH or cortisone in massive dosage in producing and maintaining a remission in the nephrotic syndrome in children and in some adults and have therefore used the same regimen in acute glomerulonephritis. An example of the response in one of the patients in the latter group is shown in Fig. 1. The term "massive dosage" should be emphasized since 25 to 50 mg. of cortisone or the same number of clinical units of ACTH per day merely exert a suppressive or displacement action without adding to the net sum of adrenocortical steroids made available to the tissues. It is our custom to give 300 mg. of cortisone or 200 units of ACTH per day in divided dosage in conjunction with a diet virtually devoid of sodium, a regimen which has proved highly effective in the therapy of rheumatic fever,[6a-c] the adult and particularly the childhood type of nephrotic syndrome,[5a-d] and of systemic lupus erythematosus, scleroderma, periarteritis, and pemphigus.[6d] This therapy, supplemented by vitamins and iron, is con-

tinued for four weeks or longer, though lesser periods may suffice. Patients on low sodium regimens must be watched for extrarenal depletion of this electrolyte via sweating or diarrhea, since this may produce convulsions, for infections such as staphylococcus bacteremia, for potassium intoxication in patients with renal failure, and for potassium depletion in those with adequate kidney function. In regard to the last point, the physician should recall that low

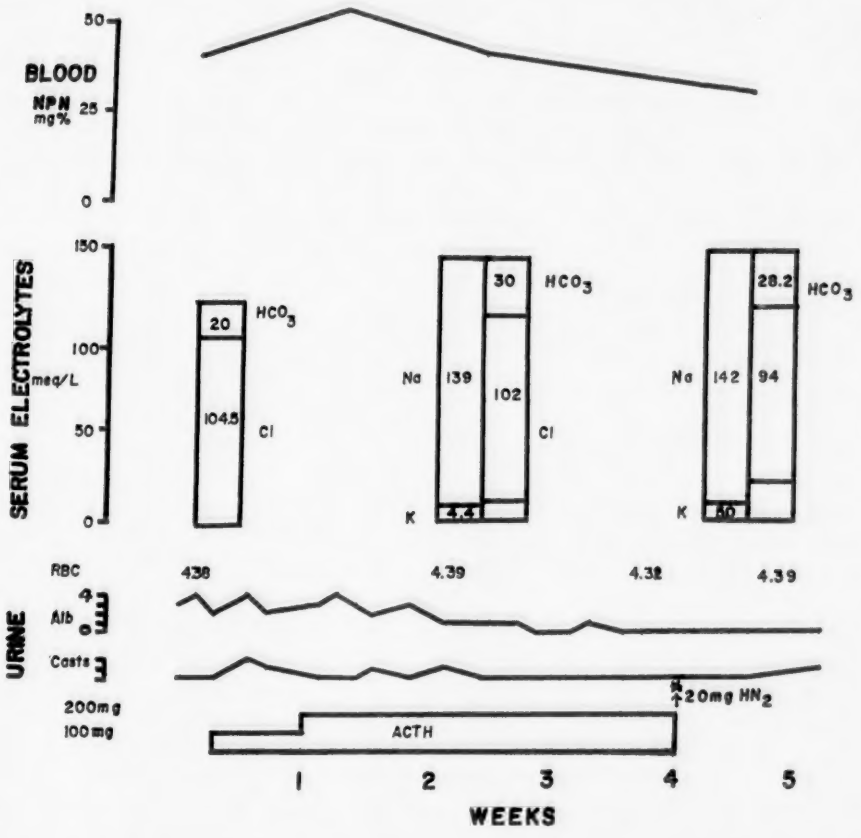

Fig. 1.—This 17-year-old school boy with history of antecedent upper respiratory infection had edema of the eyelids and feet for two weeks prior to admission. There were hypertension, edema, albuminuria, cylindruria, hematuria, slight azotemia, and elevated sedimentation rate. Hemolytic streptococci cultured from the throat disappeared after administration of penicillin. Albuminuria and azotemia subsided after therapy with sodium restriction and ACTH. Twenty milligrams of nitrogen mustard were given at the end of the fourth week.

sodium diets are high in potassium, but that potassium depletion still may develop if renal function is unimpaired. For this reason 1 Gm. of potassium chloride is given three times daily to patients with a normal nonprotein nitrogen and a good urine output.

It should be pointed out, however, that not all workers are enthusiastic about the use of ACTH or adrenocortical steroids in the treatment of acute glomerulonephritis.[7a-e] Thus, even those who have seen prompt remissions

with these agents hesitate to recommend their routine use because most patients with the acute form of the disease recover on supportive therapy only.[7e] Others feel that the patient may become worse during steroid or ACTH administration[7b] or that the hazards are too great. We feel that general use of such regimens is essential if the incidence of the chronic form is to be decreased. The so-called poor responses may be attributable to inadequate dosage stemming from failure to differentiate among displacement, replacement, and pharmacologic amounts of these agents, or may result from a failure to maintain patients on suitable electrolyte regimens during such therapy, or represent the irreversible and progressive nature of the ailment in some patients regardless of the therapy employed. It is fair to point out, however, that the statistical proof of the beneficial effects of such adrenocortical steroid therapy will require a large series of cases because the spontaneous healing rate in acute glomerulonephritis is so high.

PRESCRIPTION OF DIET, WATER, AND ELECTROLYTES IN ACUTE PHASES OF GLOMERULONEPHRITIS WITHOUT SIGNIFICANT REDUCTION OF URINARY OUTPUT OR RENAL FUNCTION

A variety of dietary regimens have been recommended, including total deprivation, for two days or longer,[8] and restriction of protein intake to 0.2 to 0.5 Gm. per kilogram to minimize the osmotic work of the kidney.[9a] We feel that the intake of food, fluids, and electrolytes should be varied in accordance with the urinary volume and the status of the body fluids. Thus, patients ill with acute glomerulonephritis or with an exacerbation during the course of chronic glomerulonephritis in whom urinary volumes are not reduced and in whom renal function is not severely compromised (i.e., blood urea nitrogen or nonprotein nitrogen is normal or only slightly above normal) may be permitted diet and fluid intake as tolerated. If edema, hypertension, or congestive heart failure is present, rigid sodium restriction must be practiced, but it is often wise to restrict sodium during the first week or two even when these signs are absent. It may be reasonable to restrict protein intake in either group of patients in the hope that responses of the type seen with the rice diet in chronic and more extensive hypertensive cardiovascular-renal disease may be evoked[10a-d] even though it is true that in some patients sodium restriction is equally effective without protein restriction. In this regard it should be pointed out that the deleterious effects of a high protein intake apart from the oft associated high intake of potassium have been demonstrated only in experimental animals with far-advanced renal failure.[9b-d] The earlier custom of treating acute glomerulonephritics with a high protein diet[9e] has been abandoned.

There is no clear indication for the use of any type of diuretic in the edema of acute glomerulonephritis, and this is especially true of mercurials and of water. Fluids should never be forced or administered in excess to patients in acute phases of glomerulonephritis. Thirst is an important guide in this regard. Otherwise water intoxication with dilution of electrolytes associated with cramps or convulsions may result. On the other hand, there is no valid basis for fluid restriction in edematous patients unless they are anuric or incapable of excreting the daily water load, since it further compromises renal insufficiency.

THERAPY OF FAR-ADVANCED RENAL FAILURE IN ACUTE OR CHRONIC GLOMERULONEPHRITIS

The appearance of renal failure in the course of acute or chronic glomerulonephritis presents the clinician with a problem which may ultimately prove of far greater importance than any of the other manifestations of these diseases. Furthermore, the changes in body fluids which appear can be equally profound in either the acute or the chronic phases and, as a matter of fact, are often indistinguishable. This is an extremely important principle, since in patients with a negative antecedent history a defeatist attitude based on the presumption that the patient is a terminal chronic uremic is sometimes unjustified. An example of this is shown in Fig. 2.

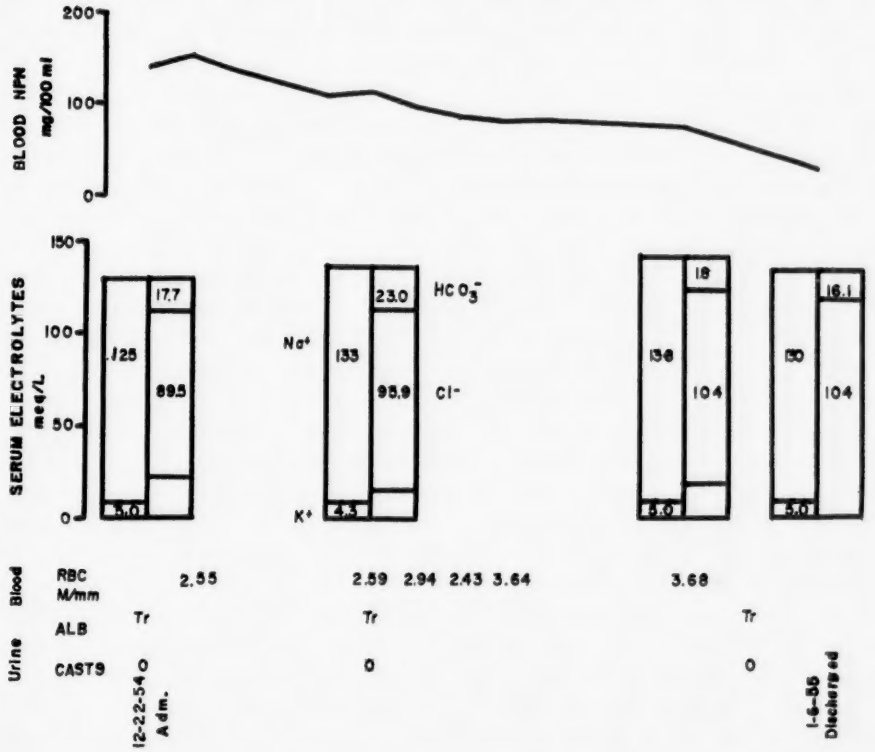

Fig. 2.—Despite the history of chronic renal disease with albuminuria for twenty-four years and the appearance of terminal uremic syndrome, this patient responded to replacement of electrolyte, fluid, and hemoglobin deficits with clinical remission and return of nonprotein nitrogen to normal concentrations.

Far-Advanced Renal Failure With Maintained Urine Output (*Table II*).—The intake of water should neither be forced nor curtailed. However, even when urine volumes are ample, the dietary intake definitely should be restricted in protein and potassium content in view of the probability that excesses of either decrease survival in renal failure.[9a-d] Rigid sodium and chloride restriction is a necessity in all cases with edema, but limitation of the intake of these two ions is probably desirable in all patients save those who are losing these electrolytes

via extrarenal routes and in those few who are excessive renal salt wasters. Such restriction of sodium postpones the onset of edema, and the diminished intake of chloride helps to minimize the metabolic acidosis which develops. The therapy of the rise in phosphate, the decrease in calcium, and the fall in serum total CO_2 content which occur in renal failure with so-called ample urine volumes is the same as in the oliguric or anuric azotemic patient and is discussed in the section which follows.

The infusion of human serum albumin or synthetic plasma volume expanders in edematous hypoalbuminemic nephritics may produce a diuresis when sodium restriction has been unsuccessful. This is especially true of the nephrotic phase,[6a-d] but the effect is, of course, transitory.

Renal Failure Characterized by Reduced Urinary Volumes (Table II).—In the actually or virtually anuric patient with acute or chronic glomerulonephritis, the input of foodstuffs should be limited to carbohydrate and fat, thereby minimizing the adverse effect of a protein load and reducing to a minimum the contribution of potassium from exogenous and endogenous sources. The intake of water should not exceed the combined volume of the urinary and extraurinary output. On such a regimen, the patient should lose a small amount of weight in the order of a few hundred grams per day. Sodium and chloride are not necessary unless significant deficits of these ions have developed because of vomiting or sweating. Even then it is wise to allow a measure of chloride deficit to persist in those patients in whom renal failure is present since, as indicated earlier, this minimizes the metabolic acidosis. Potassium and phosphate salts are, in general, interdicted since both of these constituents tend to increase in extracellular fluids during renal failure. Even though hypocalcemia develops in conjunction with hyperphosphatemia, calcium salt administration is not necessary unless tetany supervenes. In turn, tetany does not appear unless alkalinizing, i.e., sodium-containing, salts have been given. Hence it is our practice not to treat the decrease in serum total CO_2 content which characterizes progressive renal failure until hyperpnea develops. At this point sodium lactate or bicarbonate is given following prior intravenous administration of calcium salts (see Table IV for details).

The use of gastrointestinal or peritoneal lavage or of extracorporeal hemodialysis by means of an artificial kidney in far-advanced renal failure is discussed in another paper of this series. The artificial kidney is remarkably effective in restoring the concentration and, in the case of the ultrafiltrator type units, the volume of body fluids toward normal. Lavage procedures (peritoneal, gastric, isolated small bowel loop, or colonic) are considerably less efficient in this regard. However, the administration of a carboxylic cation exchange resin as a high retention enema can be quite effective in relieving dangerous hyperkalemia.[11a-e] Details of these forms of therapy, of insulin and glucose, and of calcium or sodium salts in combating potassium intoxication, are given in Tables II and IV.[11e]

Aluminum hydroxide gel may be used to increase fecal excretion of phosphate,[1b] but it may also produce gastrointestinal distress and fecal impaction.

Again, as in acute glomerulonephritis, there are no clear-cut indications for the use of diuretics in patients with severe renal failure.

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TABLE II. THERAPY OF FAR-ADVANCED RENAL FAILURE IN ACUTE, EXACERBATIVE, OR CHRONIC NEPHRITIS

FOODSTUFFS				ELECTROLYTES				OTHER MEASURES			
WATER	CHO	FAT	PROTEIN	Na	Cl	K	Ca	Hg DIURETIC	LAVAGE	DIALYSIS	CATION EXCHANGE RESIN
A. With Urine Volumes Maintained:											
ad lib (minimum of insensible loss + urine volume)	*ad lib* (minimum q. 100 Gm. q.d.)	*ad lib*	?Restrict to 0.5 Gm. per kilogram	?Restrict $\bar{s}$ edema; Restrict $\bar{c}$ edema	Restrict $\bar{c}$ or $\bar{s}$ edema	No restriction unless K in serum increased or if terminal renal failure is present. See Table IV for therapy of K intoxication	None unless alkali given or tetany develops: then give 1.0 Gm. of $CaCl_2$ or Ca gluconate I.V. at a time. See Table IV for use of Ca in K intoxication	No	For K^+ intoxication (peritoneal or gastrointestinal) (Chap. 25 ref. 11e)	In terminal phase (high NPN, convulsions, vomiting) K^+ intoxication, etc.	For K^+ intoxication see Table IV
B. In Impending or Complete Anuria:											
Enough for insensible loss not covered by H_2O of metabolism, i.e., 600-1200 c.c./24 hr. Use body wt. as index: patient should not gain weight or preferably lose 200-300 grams per day	At least 100 Gm. q.d.	As tolerated by stomach tube	None	None	None	None	None unless alkali given or tetany develops: etc. (as above)	No	For K^+ intoxication, etc. (as above)	In fifth day of anuria or with K^+ intoxication or water excess	As above

TABLE III. FREQUENCY OF NAUSEA, VOMITING, ANOREXIA, CONGESTIVE HEART FAILURE, CONVULSIONS, COMA, AND ANEMIA IN 14 ADULTS ILL WITH TERMINAL GLOMERULONEPHRITIS PROVED BY AUTOPSY

PATIENT	SEX	AGE (YR.)	NPN* (MG./100 ml.)	NAUSEA	VOMITING	ANOREXIA	CONGESTIVE FAILURE	CONVULSIONS	COMA	Hb† (GM./100 ml.)
P.M.	M	28	240	X	X	X	X	0	0	6.5
A.S.	M	34	243	X	X	X	X	0	0	8.5
V.J.	F	31	198	X	X	X	X	0	0	4.5
J.M.	F	35	200	0	0	0	X	X	X	11.5
J.M.	M	30	250	X	X	X	X	0	0	4.3
R.M.	M	54	290	X	X	X	X	0	0	8.0
F.R.	M	30	142	X	X	X	X	0	X	7.5
B.F.	M	24	250	X	X	±	X	0	0	4.0
G.T.	M	39	250	X	X	X	X	X	0	4.0
G.W.	M	31	99	X	X	X	X	0	0	6.0
C.R.	M	56	178	X	X	X	X	0	0	6.0
W.C.	M	49	220	X	X	X	0	0	X	7.0
J.B.	M	25	138	X	X		X	0	X	5.5
R.M.	M	22	310	X	X		X		X	8.9

*Highest value. †Lowest value.

TABLE IV. THERAPY OF VARIOUS MANIFESTATIONS OR COMPLICATIONS OF ACUTE OR CHRONIC GLOMERULONEPHRITIS

Potassium Intoxication

Stop all K intake;
Limit input to water, carbohydrate, fat *per os* or stomach tube;
Carboxylic cation exchange resin (H^+ or NH_4^+ form) 60 Gm. q.d. *per os* if tolerated or as a high retention enema (25-40 Gm. in 400 c.c. tap H_2O);
Vivodialysis by means of artificial kidney; gastric, gastrointestinal or peritoneal lavage less effective;
Transient lowering may be achieved by insulin (0.1-0.3u. per kilogram) and glucose (0.5-3.5 Gm. per kilogram);
Calcium chloride or gluconate 1.0 Gm. I.V. as K antagonist;
Sodium lactate (hypertonic molar lactate 11 Gm. %—100-200 c.c. I.V.) for heart block (ref. 22);
Digitalis is a K antagonist and can be administered in heart block or impending cardiac stand still.

Edema

Peripheral edema
Sodium restriction;
H_2O restriction only with oliguria or anuria;
Rx of heart failure if present;
Colloid rarely necessary;
Usually no diuretics; no Hg^{++};
Vivodialysis (see Table II)

Pulmonary edema
Prevent by limiting intake of sodium and of water in patients with limited excretory capacity;
Ganglionic blocking agents (hexamethonium 2.5-7.5 mg. I.V. c̄ patient sitting) or tourniquets to pool venous return (ref. 23);
Digitalis, O_2, aerosols.

Metabolic Acidosis

None until hyperpnea supervenes, then administer Ca gluconate or chloride 1.0 Gm. first before giving sodium bicarbonate or lactate I.V.: hypertonic $NaHCO_3$ (7.5 Gm. %), hypertonic molar lactate (11 Gm. %), or isotonic one-sixth molar lactate (1.8 Gm. %). Total amounts necessary determined by external and internal transfers of sodium and other cations, but start with 100 ml. of first two solutions or 1 liter of the last.

Hypertension

Bed rest;
Sodium restriction;
? Restriction of protein to 0.5 Gm./Kg.;
Sedation;
Antihypertensive drugs (rauwolfia, veratrum, hydralazine, as in text).

Anorexia, Nausea, Vomiting

Avoid or eliminate anorexigenic agents (digitalis excesses, iron compounds);
Chlorpromazine orally, intramuscularly, or per rectum (10-25 mg. q. 4-6 hr. P.O. or I.M.);
Refeeding within hour of vomiting may be successful;
Record intake or output and provide water in amounts to cover insensible loss, urine volume, and losses in vomitus or sweat. Sodium salts in accord with losses.

Anemia

Determine etiology;
No Rx unless RBC below 3.0 ml./mm^3 or in accord with symptomatology;
With hemolysis: cortisone, ACTH, meticorten;
With bone marrow depression: cobaltous chloride, no more than 100 mg. q.d.;
Transfusions.

Congestive Heart Failure

Therapy as in any congestive heart failure;
Bed rest, O_2;
Eliminate sodium intake;
Intake of H_2O in accord with urine volume, insensible loss, and thirst; restriction only with anuria or decreased capacity to excrete water loads;
Digitalis: rapidly excreted glycosides such as digoxin preferred; watch for Ca potentiation of and K antagonism to effects of digitalis;
Diuretics usually not indicated.
Hg^{++} to be avoided.

Convulsions

Determine etiology;
In H_2O intoxication: limit water and cautiously give NaCl, using restoration of normal Na^+ levels as index;
In salt depletion: replace salt;
In hypertensive crisis: antihypertensive agents (see text);
In hypocalcemic tetany (usually p̄ alkali Rx): calcium chloride or gluconate 1.0 Gm. I.V.;
If etiology undetermined: $MgSO_4$ infusion (see text and ref. 16b);
? Benefit from Dilantin, phenobarbital or other anticonvulsants.

Hyponatremia

Determine etiology (ref. 21);
Sodium depletion: replace sodium;
Water excesses: restriction of water intake and cautious use of sodium salts;
"New steady state," i.e., hyponatremia with increased total sodium stores resulting from resetting of regulatory mechanisms at new levels: correct renal failure; treat congestive heart failure, if present; sodium salts usually only aggravate edema, and water restriction is dangerous.

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THERAPY OF ANOREXIA-NAUSEA-VOMITING, CONGESTIVE HEART FAILURE, CONVULSIONS, ANEMIA, AND HYPONATREMIA IN ACUTE OR CHRONIC GLOMERULONEPHRITIS

Current views of the management of the common manifestations and complications of far-advanced renal failure, i.e., of "uremia" (see Table III), are outlined in Table IV and are discussed below.

Anorexia, Nausea, and Vomiting.—The spontaneous appearance of nausea and vomiting in the course of renal disease is an extremely ominous sign. Their origins remain obscure: do these symptoms result from accumulations of metabolites, from edema or petechial hemorrhages in the brain or the gastrointestinal tract, from distorted solute or electrolyte patterns, or from the effects of the last of these upon the function of organ systems? For example, does hyperkalemia potentiate vagal activity and thus lead to abnormal gastrointestinal tract motility?[13] Since nausea and vomiting interfere with intake and result in losses of body constituents, they can further aggravate the biochemical disturbance of renal failure by superimposing dehydration and depletion. In view of the serious portent and effects of these disturbances, it seems reasonable to be very cautious in using agents such as digitalis, ferrous sulfate, cobaltous chloride, or any others which can cause them.

Therapy is based on elimination of anorexigenic and emetic drugs, and the use of chlorpromazine. The dosage of chlorpromazine should be adjusted to individual needs beginning with 10 to 25 mg. two to four times daily and increasing to a total of 150 to 300 mg. each day. If the patient cannot retain the drug, it may be given as a suppository (100 mg.) or intramuscularly (25 to 50 mg.) at intervals of four to six hours. If the symptoms persist, it should be kept in mind that, in contrast to the nausea and vomiting of acute gastroenteritis, which are best treated by restriction of all intake for twelve hours or longer, in renal failure the patient is often willing and should be allowed to resume oral intake within an hour or less of a vomiting episode.

Congestive Heart Failure.—In patients with acute or chronic glomerulonephritis edema, expansions in plasma volume and venous distention may only represent alterations in body fluid comportments secondary to renal failure rather than congestive heart failure.[18a-c] A minority of the patients with acute glomerulonephritis and a larger proportion of those with chronic nephritis develop symptoms and signs of true congestive heart failure,[18a-d] though many more show radiologic or electrocardiographic evidence of circulatory system involvement. True congestive heart failure occurring in acute or chronic glomerulonephritis should be treated as in any other patient save that the antagonism between hypocalcemia or hyperkalemia and digitalis effect, and accentuation of digitalis action by deficits of potassium or excesses of calcium, are more apt to be encountered.[14a-c] For this reason more rapidly eliminated digitalis glycosides such as digoxin should be favored, since they simplify adjustment.

Convulsions.—Convulsions which originate from water intoxication (i.e., from excesses of water or, less often, from depletion of sodium) can be treated with hypertonic sodium chloride (200 to 500 ml. of a 2 to 5 per cent solution given slowly by vein) although this will of course aggravate any edema. Tetany

or hypocalcemic seizures are almost always the result of excessive alkali administration and require therapy with intravenous calcium. A 20 ml. ampule containing 1 Gm. of calcium gluconate or calcium chloride, 1 Gm. in a volume of 10 ml., often suffices but may be repeated if necessary. A favorable response is not incontrovertible evidence that the convulsions were of hypocalcemic origin, since increasing the concentration of calcium in subjects without depletion of these ions also raises the threshold for convulsive seizures.[15a]

Convulsions associated with hypertension may respond to therapy with antihypertensive drugs.[15b-e] Derivatives of rauwolfia induce sedation, bradycardia, and hypotension but are not so effective as the veratrum group. Of the latter, protoveratrine, a pure alkaloid, is particularly useful at a dosage of 0.25 mg. every six hours. Toxicity consisting of nausea and vomiting must be guarded against. Hydralazine, 10 to 50 mg. four times daily, may prevent convulsive seizures associated with hypertension. The hexamethonium compounds have a profound hypotensive effect and cause gastrointestinal side reactions which make them of limited use, if any, in the therapy of patients with renal failure. They are useful, however, in pulmonary edema (Table IV).

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Most seizures, however, cannot be attributed to any of the above causes. They are to be treated with anticonvulsant agents such as phenobarbital or Dilantin, though the evidence that these latter agents decrease the incidence of convulsions in renal failure is not definitive. To control convulsions Rubin and Rapoport,[16a] Winkler, Smith, and Hoff,[16b] and others[16c-f] have used infusions of magnesium sulfate (500 ml. of a 2 per cent aqueous solution given rapidly intravenously followed by an additional 100 ml. or more infused slowly[16b]) to the point of extinction of the knee jerks. The margin between this end point and respiratory failure is so small that this is of necessity a dangerous procedure. The custom of intramuscular injections of this salt in lesser amounts is useless.

Anemia.—The anemia which develops in renal failure could result from (a) transfers of interstitial and cell fluid into the circulation with resultant overexpansion of the circulating plasma volume (as demonstrated by Brown and associates[17a] in acute experimental anuria of animals), (b) an increased hemolysis of blood cells with or without a positive Coombs test, increased urinary urobilinogen excretion, and a rise in the reticulocytes, (c) decreased red cell survival, (d) a terminal depression of erythrocyte production by the bone marrow, or (e) combinations of the above. According to the findings of Callen and Limarzi[17b] the anemia when present is most often of the normochromic normocytic type, macrocytic in a minority of cases, and only rarely microcytic and hypochromic. The bone marrow is hypercellular in 80 per cent of the patients with nonprotein nitrogen values which are elevated, but less than 150 mg. per cent. This increased cellularity involves chiefly the myeloid and megakaryocytic cells, while erythropoiesis is normal. With nonprotein nitrogen levels above 150 mg. per cent, quantitative and qualitative hypoplasia of the erythroid elements is observed. These findings suggest that diminished production is a common feature of far-advanced renal failure, but shed no light on the possible role, if any, of the other factors.

The degree of anemia and symptomatology should determine therapy. Reduction of the erythrocyte count to three million per cubic millimeter with

comparable decrease in hemoglobin requires no therapy. It is also obvious that transfusions of blood or erythrocytes are not indicated in anemias resulting from overexpansion of extracellular fluid of the type which can occur in acute glomerulonephritis or in anuria. If the presence of an acute hemolytic process can be demonstrated by means of the indices cited, it should be treated with cortisone or other adrenocortical steroids.[18a-c] Transfusions can be administered to patients with decreased red cell survival or with failure of erythrocyte production. In some of the patients with chronic uremia or anemia a rise in red cell production may be obtained by cobalt therapy,[19a-e] though the danger of inducing nausea and vomiting,[19b] cited earlier, must be kept in mind. These last two procedures are relatively safe. There is probably a lower incidence of reactions to transfusions in uremic patients and the cobalt-induced goiter[20a-c] is a relatively minor matter in these seriously ill patients. However, it is our impression that restoration of erythrocyte counts to normal by any of these means usually does nothing for the underlying renal failure, though fatigability, dyspnea, or other symptoms arising from anemia per se do respond.

Hyponatremia.—In the terminal phase of renal failure many patients develop hyponatremia. If salt depletion and water intoxication can be excluded as etiologic mechanisms, this hypotonicity can be taken to represent a new steady state,[21] i.e., a resetting at these new levels of the homeostatic mechanisms controlling volume and concentration. In such cases therapy with sodium produces only a transient rise in serum levels and ultimately aggravates the edema. Often, however, a therapeutic trial is the only way in which the possibility of sodium depletion can be excluded. Vivodialysis via an artificial kidney of the ultrafiltrator type is effective in correcting the hyponatremia and edema, but the improvement is transient.

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THE USE OF THE ARTIFICIAL KIDNEY IN THE TREATMENT OF GLOMERULONEPHRITIS

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THE title of this paper is perhaps misleading, for in the employment of the artificial kidney to treat patients with glomerulonephritis we are in fact not treating the disease itself. We are treating the abnormality in composition of body fluids which results from failure of kidneys severely damaged by glomerulonephritis. In this sense, the artificial kidney is a tool for the treatment of chemical rather than organic abnormalities. It does nothing for the kidney disease per se. Since, however, the morbid state resulting from glomerulonephritis, either acute of chronic, may in large part be due to the resultant renal failure, the artificial kidney may be valuable in these instances. We will outline its use in the management of three distinct phases in the natural history of glomerulonephritis:

1. The artificial kidney may modify the severe renal failure that occurs in acute glomerulonephritis until such time as spontaneous healing of the renal lesion takes place.

2. Exacerbations of glomerulonephritis resulting in renal failure may be treated with much the same rationale as the initial acute attack. Since it is generally believed that exacerbations of glomerulonephritis do not affect the rate of progress of the underlying lesion, it would be important to control an acute bout of renal failure during an exacerbation in the expectation that more normal renal function will exist after the exacerbation has run its course.

3. There are three uses for the artificial kidney in chronic renal failure (a) It may be used to treat the patient following decompensation from intercurrent infection or trauma, where renal reserve is not adequate to cope with these stresses. (b) It may be of value in ameliorating the nausea, anorexia, and vomiting which interfere with adequate fluid, electrolyte, and caloric intake in patients with chronic glomerulonephritis whose course has been gradually downhill. (c) It may be employed to improve the clinical status of patients with chronic glomerulonephritis and renal failure in preparation for necessary surgery or following surgical procedures where decompensation has occurred. These indications will be considered in greater detail below.

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Let us consider now what an artificial kidney actually is. To understand this we must first comprehend the principle of dialysis upon which all such apparatus depend. Visualize a vessel divided into two compartments separated by a semipermeable membrane such as cellophane. In compartment A is an aqueous solution containing both crystalloids and colloids. In compartment B there is only water. Owing to the concentration gradient across the membrane, water will tend to diffuse into the solution and the solutes into the water compartment. Since the pore size of cellophane is such as to impede the transfer of the colloids, but not of the crystalloids, only water and crystalloids will pass from one compartment to the other. Such a situation is known as differential diffusion, or *dialysis*. The colloidal solutes (such as blood proteins) would be retained. If the membrane were impermeable to all solutes so that the only diffusion occurring was that of water into the solution, the process would be ordinary *osmosis*. If, in addition, we increased the hydrostatic pressure in compartment A so that it exceeded the osmotic pressure of the solution (tending to draw water into compartment A), there would be a net flow of water out of the solution compartment and *ultrafiltration* would have taken place.

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CELLOPHANE AND GLOMERULUS AS SEMIPERMEABLE -MEMBRANES

	CELLOPHANE	GLOMERULAR CAPILLARY
Fractional pore area	30-45%	.01%
Total area	22,000 cm.² (rotating model)	7,600-15,000 cm.²
Pore radius	30 Å	30-45 Å
Pore length	80μ	1μ

(Pore radius of 100-120—95% albumin permeable)

Fig. 1.

There are various types of artificial kidneys, all of which employ cellophane membranes and the principle of dialysis. Some artificial kidneys contain the cellophane membrane within a wire mesh or plastic pad so that the hydrostatic pressure inside the pliable membrane may be increased. Under such circumstances ultrafiltration is possible. Fig. 1 compares cellophane and normal human glomerulus as semipermeable membranes. It will be seen that the fractional pore area (that is, the area actually available for passage of solute molecules) is considerably larger in the cellophane membrane. The total area of one type of artificial kidney, the rotating or Kolff-Brigham model, contains a total surface area actually bigger than the total glomerular capillary area. The pore radius, or the radius of the theoretic pores in the cellophane membrane, is about the same as that calculated for the glomerular membrane. It will be seen that in both instances these are small enough so that they would retain the albumin molecule. The cellophane, however, has a pore length much greater

than the glomerular membrane, and this, of course, is a decided disadvantage since the solute particles must traverse a much greater distance in their passage from the blood plasma. The artificial kidney has one great advantage over the mammalian nephron in that it has no tubules. Solutes, such as sodium, filtered at the glomerulus are resorbed into the peritubular plasma by the tubule, and under abnormal circumstances this may be difficult to control. The transfer of solute across the cellophane membrane of an artificial kidney, however, is governed solely by the concentration gradient on either side of the membrane. Thus, if we pass blood through a cellophane tube surrounded by a properly constituted bath fluid, and if in this bath fluid we lower the sodium concentration below that of the circulating blood, sodium will pass from blood to bath because of the difference in concentration.

Similarly, if the chloride concentration of the bath fluid is higher than that in the blood, chloride will pass from bath to blood because of its concentration gradient. Both these solutes may pass in opposite directions at the same time, the direction and rate of their transfer being governed entirely by the individual concentration gradient. Since these transfers are governed by predictable physical laws, we can thus accurately effect removal or addition of diffusible solutes to circulating blood during its passage through an artificial kidney.

BATH COMPOSITION

	GM./100 L.	MOSM./L.	MEQ./L.
NaCl	600	205	102.5
$NaHCO_3$	290	69	34.5
KCl	30	8.0	4.0
$MgCl_2 . 6H_2O$	10	1.5	1.0
$CaCl_2 . 2H_2O$	18.5	3.8	2.5
Glucose	200	11	
		298.3	$Na^+ = 137$ $Cl^- = 110$

Fig. 2.

In the treatment of renal failure with such a technique we are usually concerned with the removal of retained metabolites so that the bath fluid is normally constituted with regard to essential electrolytes. The notable exception is the potassium concentration of the bath, since hyperkalemia may be one of the complications of renal failure in which an artificial kidney is most effectively employed. Fig. 2 shows the composition of bath fluid utilized by most workers in this field. The sodium and chloride concentrations are approximately normal, as is the total osmolarity. Extra glucose may be added to increase the osmolarity if, as is frequently the case, the plasma osmolarity in renal failure is increased. Since the membrane is permeable to glucose, however, the contribution of glucose

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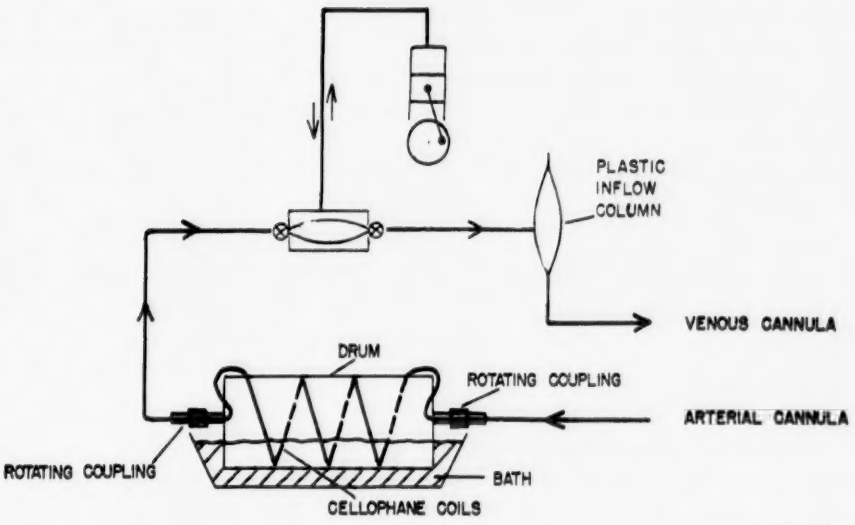

Fig. 3.—In the modified rotating artificial kidney, blood is passed through a rotating coupling into cellophane tubing spirally wrapped upon a rotating drum. The drum is partially immersed in bath fluid and the clockwise rotation of the drum propels the blood from the arterial to the venous end during which time transfer of solute takes place from blood to bath across the semipermeable cellophane membrane. The blood is then returned from the venous end of the apparatus into a peripheral vein by means of a pump.

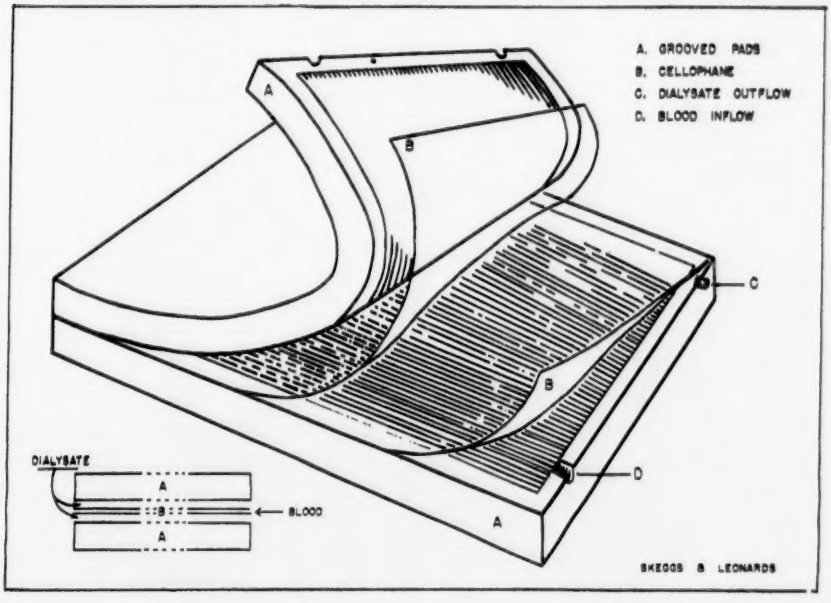

Fig. 4.—A schematic representation of one unit of the Skeggs-Leonards stationary artificial kidney. Blood flows between the cellophane sheets (B - B), which are sandwiched between grooved plastic or rubber pads. The rinsing fluid passes on either side of the cellophane sheets through the grooved channels. In clinical use, several of these units are manifolded together. This type of artificial kidney, because of its rigid supporting structure, may be used as an ultrafilter when the hydrostatic pressure within the cellophane is greater than that of the surrounding rinsing fluid.

in the bath fluid to its osmolarity is maintained only transiently, but the loss of glucose to the blood from a 100 liter bath does not affect the bath composition markedly and the increasing blood glucose concentration is probably counterbalanced by loss of a diffusible solute such as urea. As will be noted subsequently, the composition of the bath should not necessarily be "normal" when we are treating chronic and markedly abnormal derangements of the chemical composition of extracellular fluid in uremic patients.

Blood from the patient's artery, usually the radial, is taken by cannula and passed through the cellophane membrane of the apparatus. During this passage, transfer of solutes occurs across the cellophane membrane into the bath fluid. The blood is then returned from the distal part of the apparatus into a convenient vein. In order to prevent clotting in the apparatus, heparin is administered before and during the procedure. Two types of artificial kidneys currently employed in hemodialysis are shown in Figs. 3 and 4.

CHANGES IN BLOOD CONSTITUENTS DURING DIALYSIS

K.B. ♀ 35 — Anuria, ? Cortical necrosis (post partum)

	INITIAL	FINAL
Hematocrit	32	33
Sugar (mg. %)	151	165
Serum Na (meq/l.)	108	130
Serum K (meq./l.)	7.3	5.1
Serum Cl (meq./l.)	76	106
CO_2 (mM/l.)	16.1	19.7
Ca (meq./l.)	3.7	5.1
NPN (mg. %)	162	64
BUN (mg. %)	72	48
Uric acid (mg. %)	18.7	6.7
Serum inorganic P (mM/l.)	3.8	1.9

Total NPN removed 35.1 Gm. (6 hours)
Total urea removed 28.3 Gm.

Fig. 5.—By properly adjusting the bath composition, abnormalities in the chemical composition of the extracellular fluid may be corrected independently. Thus it will be noted that the serum sodium concentration is increased at the same time that the potassium concentration is decreased. Similarly, chloride concentration is increased while nonprotein nitrogen, blood urea nitrogen, and uric acid are all decreased. Because of the dependence of solute transfer upon concentration gradient, the direction in which net transfer occurs for each ion and molecule is independent of the direction and rate of transfer of any other substance.

The artificial kidney is an extremely effective apparatus for the removal of diffusible solutes. Indeed, its urea clearance at blood flows of 200 c.c. per minute equals or exceeds the normal urea clearance. Abnormalities in the concentration of nitrogenous metabolites and of electrolyte (whether they be initially elevated or depressed) may be rapidly returned to normal. Fig. 5 shows changes effected in a typical six-hour procedure. Under such circumstances nausea and vomiting may disappear and the apathetic, comatose patient may become alert and cooperative. The general improvement in well-being greatly facilitates conservative forms of medical management.

In spite of intensive interest and investigation, we still are ignorant of the specific chemical abnormalities to which we may relate the morbid state in renal failure. Although blood urea nitrogen may be rapidly lowered by dialysis, this has very little, if any, effect upon the clinical status. Urea does not appear to be a toxic substance per se and, indeed, failure to lower blood urea nitrogen levels during dialysis in which urea is placed purposefully in the bath results in clinical improvement indistinguishable from those procedures in which urea is removed. Other diffusible metabolites present in abnormal concentrations are removed, but to no specific one of these can we attribute the improvement. The removal of phosphate, sulfate, the various amino acids, organic acids, and probably catecholamines can be accomplished by dialysis with the artificial kidney. Potassium may be removed, sodium added, and chloride replaced. But to no single one of these effects can we attribute improvement. If any one parameter can be implicated, it appears that the closest correlation is with the amelioration of acidosis.

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ACUTE GLOMERULONEPHRITIS

Indications for the use of the artificial kidney in acute glomerulonephritis are rare. It is indicated only when there is marked nitrogen retention (with or without acidosis) and clinical deterioration which appears to depend upon chemical abnormalities rather than upon hypertension or congestive heart failure. In children particularly, even in the presence of severe degrees of nitrogen retention, spontaneous healing and improvement is the rule rather than the exception, and dialysis should not be hastily undertaken. In an occasional child and more frequently in adult patients, the clinical and chemical improvement attendant upon the use of the artificial kidney may warrant its use. In such instances, however, the therapist must proceed with extreme caution, since the addition of sodium and water from the bath fluid may further aggravate edema, hypertension, and congestive failure. Under such circumstances hypertensive encephalopathy and convulsions may result. The composition and tonicity of the bath fluid in such instances should be carefully adjusted to prevent the addition of excess sodium and water. The use of the artificial kidney in patients with acute glomerulonephritis should be reserved for those patients whose nitrogen retention is marked enough so that in spite of good conservative measures they are gravely ill or show evidence of potassium intoxication. In such cases, as in other instances of acute renal failure, the use of dialysis may tide the patient over until renal function improves. In the adult, prolonged and extreme oliguria, and particularly anuria, has frequently, in our experience, been inconsistent with recovery. Thus, while one or two dialyses may be undertaken with the expectation of return of renal function, in some patients with prolonged anuria repeated dialysis may be a fruitless effort. Several such patients maintained by dialysis have survived 30, 60, and even 87 days of total anuria, after which time autopsy revealed that all the glomeruli had been obliterated by the disease. In such instances renal biopsy has proved an extremely useful and important technique in ascertaining whether the possibility of resuming renal function justifies continued treatment with the artificial kidney.

EXACERBATIONS OF GLOMERULONEPHRITIS

The indications and contraindications for use of dialysis in exacerbations of glomerulonephritis are essentially similar to those of the acute state. Its use under these circumstances is predicated upon the fact that the patient may die of the derangements of chemical composition of the extracellular fluid resulting from the acute but temporary loss of renal function. In our experience, a few such cases have apparently been greatly benefited by dialysis, but again good conservative management seems adequate in most cases.

CHRONIC GLOMERULONEPHRITIS

The patient in renal failure as a result of chronic glomerulonephritis (or from any other chronic renal disease) is in a state of precarious balance. Compensatory mechanisms which have enabled him to adjust for progressing abnormalities of his chemical environment may serve well enough in the steady state, but they can be overwhelmed by sudden trauma or infection. Under these circumstances he may "decompensate." Although the patient with chronic renal failure frequently tolerates surgery and trauma better than one might expect, recovery from this exogenous insult may be impeded by the rapid progression of the signs and symptoms of uremia. In such instances conservative measures may be inadequate. More important, perhaps, is that each day "decompensation" is allowed to persist, the chances of recovery may decrease. In such instances the restoration of balance by dialysis with the artificial kidney may be of real value. It is difficult to assess statistically the value of such a procedure under these circumstances, since only critically ill patients need be treated, and in such a group the mortality is always great. The situation is analogous to that of acute renal failure complicated by trauma or major surgery in which the use of hemodialysis is an adjunct rather than a substitute for other forms of therapy.

Even without additional stress, there comes a time in the course of some cases of chronic renal failure where the compensatory mechanisms are no longer adequate for maintaining well-being. Nausea, vomiting, or anorexia intervene. These preclude the ingestion of adequate calories and fluid, and this defect, in turn, aggravates nitrogen retention, decreases filtration rate, and institutes a vicious circle. In many such cases, the onset of "decompensation" may be so sudden as to simulate acute renal failure from other causes. In one patient seen recently, the first overt symptom was precordial pain simulating myocardial infarction but in reality due to the onset of uremic pericarditis. In such patients, rehydration and the restoration of fluid and electrolyte balance may cause clinical improvement. If they fail to do so, or progress appears too slow, marked symptomatic improvement may be effected in certain cases by dialysis with the artificial kidney. The selection of such cases for treatment must be carefully made. The effects to be expected are amelioration of nausea and vomiting, improvement in appetite and strength, and correction of apathy, weakness, and drowsiness. We know that these symptoms may be ascribed to chemical defects although we cannot delineate the specific defects. We know this because improvement in

these parameters follows dialysis with the artificial kidney, whose only function is to correct chemical defects. This form of therapy cannot cure congestive heart failure or hypertensive disease. In instances where the morbid state may be more properly ascribed to cardiovascular involvement, dialysis has no place in treatment. In most patients with chronic renal failure from any cause, the prognosis is determined not so much by the extent of the renal lesion as by the degree of cardiovascular involvement. The patient with a good urine volume and the ability to handle an intake high in sodium can usually be managed by conservative means. In such a patient, when decompensation occurs (as a result of fluid or electrolyte imbalance), the response to the repair of sodium and water depletion is usually gratifying. Unfortunately, in many patients with chronic renal failure, and particularly in those with chronic glomerulonephritis, the advent of hypertension with cardiovascular impairment is a limiting factor. The ability to tolerate sodium and water loading is impaired and such patients must be carefully titrated between renal failure and congestive heart failure. In a small group of such patients, dialysis with the artificial kidney may result in clinical improvement without resort to the hazardous necessity of increasing fluid and electrolyte intake.

Remissions achieved by dialysis in these instances are difficult to predict. In general, the more advanced the cardiovascular disease and the poorer the urine volume, the shorter the clinical remission. Oliguria with advanced congestive heart failure predicates improvement of such short duration as to make the procedure worthless. However, we have seen patients with mild congestive heart failure and urine volumes of over 1,500 ml. per day in whom hemodialysis has relieved intractable anorexia and nausea and permitted many months of useful living.

The effects of dialysis in the treatment of chronic uremia tell us much about the nature of the syndrome. We have learned that patients with chronic compensated renal failure should not be "rapidly readjusted." The abnormalities that we measure in the extracellular fluid do not necessarily reflect those in the intracellular compartment. Hyponatremia and hyperkalemia, for instance, in the chronic compensated patient may not necessarily need correction. The relative concentrations of sodium and potassium in intracellular and extracellular fluid appear to depend upon energy derived from normal metabolic processes which maintain a gradient for these ions across the cell membrane. When these normal metabolic processes are upset by the severe chemical abnormalities of body fluids in uremia, the mechanisms which regulate the concentrations of sodium and potassium are reset. Under these new circumstances, then, hyponatremia and hypokalemia reflect abnormalities dependent upon more fundamental defects in metabolism, and perhaps we should not attempt to readjust these concentrations until the more fundamental defect (uremia) has been remedied. We have found that dialysis in such patients is more effective if performed in two stages. The first period lasts for only two to three hours, and during this time the concentration of the sodium in the bath is deliberately set to match the low concentration of the extracellular fluid. After a period of five or six days the second procedure is carried out, at which time more extensive

corrections are effected. The rationale behind such a method of treatment is as follows: In any chronic disease, changes which have occurred over months or years should not be totally corrected in a matter of hours. Compensatory mechanisms, including complex intracellular buffers, have gradually acclimatized the patient to these changes. A beneficial response to the rapid reversal of such changes by hemodialysis cannot be expected in a matter of hours. One of the most striking phenomena observed in eight years of experience with the artificial kidney is the fact that despite the rapid reversal of blood chemical abnormalities to normal or near normal values following the use of the artificial kidney, clinical improvement in chronic uremia may not begin for forty-eight hours and may not be maximal for four to five days.

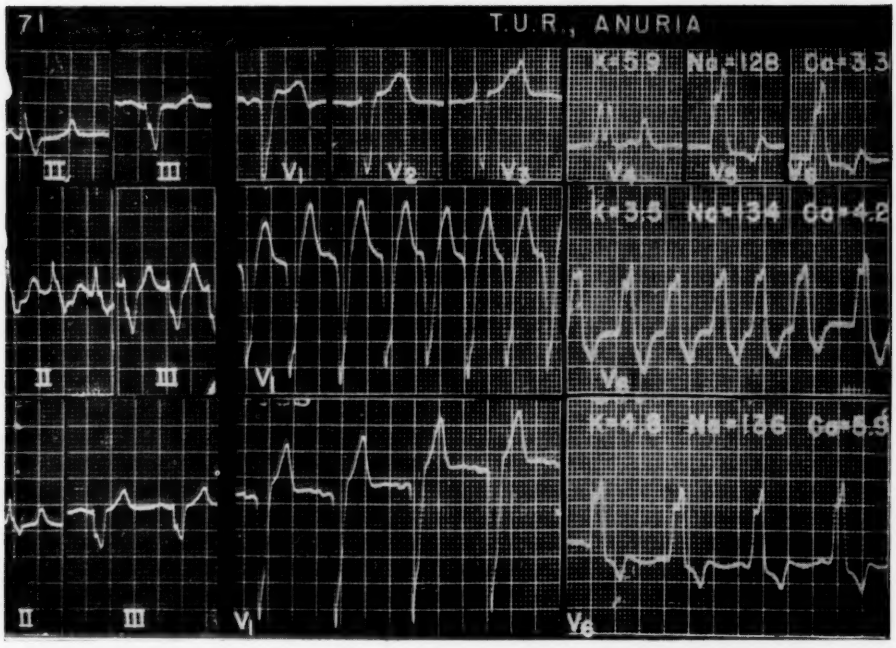

Fig. 6.—The development of superventricular tachycardia during the course of hemodialysis in a patient with bundle branch block. This development during a procedure in which serum sodium and calcium are rapidly increased and serum potassium decreased is not uncommon and may have serious consequences if unrecognized. In this instance it was reversed by adding potassium to the bath fluid.

In chronic renal failure successive treatments with the artificial kidney are indicated if nausea, vomiting, apathy, and weakness recur in the absence of marked cardiovascular impairment. Usually, however, subsequent treatments are less effective in causing remission than is the first and it has rarely been worth while to employ this procedure more than three or four times in chronic renal failure.

The hazards of effecting too rapid changes in the composition of body fluids is attested to by the frequency with which cardiac arrhythmias, parti-

cularly in the digitalized patient, may occur during the course of effective hemodialysis. These arrhythmias occur frequently during the first procedure, rarely during the second or third. They are seldom dangerous if the chemical changes are not too rapid or prolonged and if one takes frequent electrocardiographic tracings so that the procedure may be terminated in time. These arrhythmias graphically indicate, however, the hazards of effecting rapid changes in the composition of extracellular fluid in uremia (Fig. 6).

From the foregoing, it should be apparent that the proper use of the artificial kidney in the treatment of glomerulonephritis with renal failure requires more than a knowledge of the technique and the apparatus. The physician employing such a therapeutic approach must be throughly familiar with the disease and its vagaries, with the clinical course of renal failure, and with the correct conservative measures and the results to be expected therefrom. He should also be aware of the intricate compensatory mechanisms for adjustment to chronic uremia and the hazards of violently readjusting these by artificial means. Above all, he should have a sense of *when not to treat.* In chronic renal failure the artificial kidney may effect dramatic, but always temporary, improvement. The decision as to when and whether to effect such temporary improvement demands an understanding not only of the disease but of the patient.

Contraindications to the use of the artificial kidney are bleeding from the gastrointestinal tract and severe congestive heart failure. Because of the necessity of heparinizing the patient for dialysis, gastrointestinal bleeding is a major hazard. Severe cardiac decompensation increases the hazards of dialysis because of the difficulties incumbent upon minor changes of blood volume that may occur. Dialysis corrects only chemical defects and as such can be expected to ameliorate the morbid state when it is due to chemical adnormalities alone. Frequently, patients with severe heart failure, with peritonitis, with overwhelming sepsis, or pneumonia may also manifest renal failure. In such instances, the artificial kidney can only be expected to be of benefit in so far as the renal failure contributes to the clinical abnormalities.

In recent years there has been a tendency to stress the virtues of small, inexpensive, "easy to use" artificial kidneys. Even if such an apparatus were to be made generally available, and to date it has not been, its widespread dissemination would not be necessarily beneficial. The ability to avoid complications in this procedure and a knowledge of the precautions to be taken, not with the apparatus but with the human organism, require experience and a thorough knowledge of the pathophysiology of renal failure. As in so many other therapeutic techniques, it is therefore not the instrument but the operator who is the limiting factor in its efficacy.

SUMMARY

The dynamics of hemodialysis, with the artificial kidney employing a cellophane membrane, are described. The artificial kidney may be of therapeutic benefit in acute glomerulonephritis and in exacerbations of glomerulonephritis when it is employed to modify the severe renal failure until such time as spontaneous healing of the renal lesion occurs. In chronic glomerulonephritis, it may be used to ameliorate acute decompensation secondary to infection, dehydration,

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surgery, or trauma. In other instances of chronic renal failure, dialysis may cause temporary remission when conservative measures have failed, providing the renal failure and not accompanying cardiovascular disease is primarily responsible for the morbid state. The successful operation of an artificial kidney requires more than possession of the apparatus, and its successful use depends upon the skill and experience of the operator.

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TRANSPLANTATION OF THE HUMAN KIDNEY

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IN SPITE of the vast literature on the etiology, experimental production, clinical course, and treatment of glomerulonephritis, we cannot "cure" the underlying lesion. This may heal spontaneously or progress insidiously to chronic disease and, while we may slow or prevent its advance, our therapy for the underlying lesion is not specific. Once there is renal failure, therapeutic efforts are limited, as they are in renal failure caused by any chronic renal disease, to the treatment of the manifestations and to efforts to aid the damaged organ to perform its essential functions. To date, we have not been able to "cure" renal failure in the same sense that we can cure pneumonia or appendicitis. Frequently we have said or thought, "We cannot give this patient new kidneys."

An interesting, although highly experimental, approach to the "cure" of renal failure has been the recent attempts to do just this; to give the patient a "new kidney." Since elective unilateral nephrectomy carries an extremely low mortality and since one healthy kidney is compatible with normal life span, the successful transplantation of a normal kidney to an individual with little functioning renal tissue should enable both the donor and recipient to survive normally.

To understand the basic problem of kidney transplantation, we must understand something about why tissue in general fails to survive when transplanted from one individual to another, since the mechanism for the rejection of kidney transplants is similar to that for the rejection of skin transplants or other grafts. A word about terminology. A *heterograft* is the transplantation of tissue from one individual to another of different species. An *autograft* is the transplantation of tissue from one portion of an individual to another portion of the same individual. Such transplants should survive normally. The *homograft*, with which we are primarily concerned, is the transplantation of tissue from one individual to another of the same species. With the possible exception of corneal transplants and the few specific instances to be mentioned below, homografts do not survive permanently except in identical twins. The reason for this is at present not well understood. Circulating antibodies cannot be demonstrated, although recent work suggests that the homograft is rejected because of an antigen-anti-

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body response which depends upon the production in the recipient of sensitized lymphocytes or plasma cells.[1] The sloughing of skin transplanted from one normal man to another occurs within a space of three to four weeks and appears to be dependent upon the production of antibodies and the sensitization of tissue cells. The role of gamma globulin in this antibody production has been clearly suggested by the fact that skin transplants will take permanently in individuals with congenital agammaglobulinemia.[2] Attempts to modify this rejection by means of anthihistamines or by cortisone in either animals or man have not been successful. The development of this immune response to transplanted tissue depends upon some degree of cellular maturity. In some fascinating experiments, tissue cells from animal A injected into animal B while it is still an embryo enable animal B after birth to tolerate homografts from animal A.[3] The injection of tissue cells after birth does not modify the response to subsequent homografts of normal tissue although they may do so in the case of transplanted tumor tissue.

Efforts to transplant kidneys in animals have met with similar failures in spite of many modifications of technical and experimental approach. In dogs, kidney homografts may function for three to eight days and may produce considerable quantities of urine. At the end of this period, however, renal function fails suddenly and the kidney is rejected. Small vessel thromboses and infiltration of the organ with plasma cells occur at this time, similar to the rejection response seen in transplanted skin. Several attempts at homotransplantation of kidneys between humans have been made, but without success. Hume, Merrill, Miller, and Thorn[4] reported a series of nine cases of homotransplantation in the human. Six of the donor kidneys were taken from cadavers shortly after death and three were removed from normal donors whose kidneys were necessarily removed during the course of other operative procedures. Four of nine transplants developed measurable function and two of these developed enough function over a long enough period of time to be of clinical benefit to the patient. One such kidney functioned well for 180 days. In the end, however, all were rejected. These experiments demonstrated that the procedure was technically feasible in the human and that the duration of function in the transplants was far longer than could be expected from the animal studies. The possibility that the immune reaction responsible for rejection in these cases was modified by the chronic illness of both donors and recipients is a real one. Certainly antibody production and the immune response appear to be modified in chronic renal failure. In this regard it is of interest that transplanted skin survives much longer in the chronic uremic patient than it does in the normal individual.

Since, the rejection of a homograft appears to be due to individual specificity, it is conceivable that tissue of monozygotic (identical) twins might be specific for both individuals since the tissue arises from a common ovum. This hypothesis has been proved by the successful homografting of skin between identical twins.[5] Since the rejection responses to skin and kidney seem similar and since sensitization of the recipient by prior transplantation of skin from a donor will cause accelerated rejection of a kidney from the same donor, it appears that skin and kidney share a common antigen responsible for the rejection response. It therefore seemed probable that if skin could be transplanted between identical

twins, kidneys could be successfully grafted also. We have recently had the opportunity to transplant a normal kidney from one identical twin to his brother who was terminally ill with chronic glomerulonephritis, advanced renal failure, and hypertension.[6] This kidney has functioned successfully in the recipient for the last sixteen months (Fig. 1). With its successful function, all the stigmata of chronic renal failure disappeared. An important additional finding was the disappearance of hypertension and all evidence of cardiovascular disease. That this occurred with the addition of a third normally functioning kidney to two badly damaged kidneys is of significance in our thinking about the etiology of renal hypertension. Two subsequent cases of homotransplantation of the kidney between identical twins have produced similar results. Although the transplantation of tissue between monozygotic twins cannot truly be called a homotransplant, the procedure is certainly feasible. The dividends to be obtained both in terms of the therapy of kidney disease and of malignant hypertension with renal involvement have been described.

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Fig. 1.—Intravenous pyelogram on homotransplanted kidney and diagrammatic sketch of kidney outline. The homotransplanted kidney, increased in size by about 30 per cent, is placed in the right pelvic fossa. A ten-minute film shows the dye to be excreted promptly and in good concentration, although the calyceal pattern is obscured by the bony detail of the pelvis and sacrum. The ureter is somewhat dilated, but this is common in a denervated ureter. (From Merrill, J. P., Murray, J. E., Harrison, J. H., and Guild, W. R.: Successful Homotransplantation of the Human Kidney Between Identical Twins, J.A.M.A. 160:277, 1956.)

In spite of these dramatic results, however, the problem of tissue homotransplantation in general and of kidney homotransplantation particularly remains unsolved. The problem is one of modifying the fundamental immune individual-specific response to the transplantation of tissues from another individual. Recent attacks on this problem by the use of whole body x-ray and and by the injection of donor tissue to "desensitize" the recipient and to enhance the survival of transplanted tissue may lead to ultimate success in this fascinating and important field. Until much greater progress is made, however, the homotransplantation of kidney in the human must remain an experimental procedure whose therapeutic value is at best a temporary one.

SUMMARY

Transplantation of the human kidney between identical twins has been successfully performed, with the attainment of normal renal function in the transplanted organ over a period of sixteen months. In other instances of homotransplantation of the kidney, function has been maintained for a longer period than in the experimental animal, but in all cases it has eventually ceased. The rejection of a transplanted kidney and of other tissues appears to depend upon an antibody response against the graft which is individual-specific. Before kidney transplantation can be of therapeutic value, means must be found to modify this "immune" response.

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THE PRODUCTION OF GLOMERULONEPHRITIS BY IMMUNOLOGIC METHODS

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GROUP A streptococci are accepted as the chief cause of human acute glomerulonephritis. The type XII strain has proved to be the most nephritogenic.[1] Although the initiating agent is known, the pathogenesis of the disease is not determined. The precipitating infection commonly occurs in the upper respiratory tract, and hemolytic streptococci usually can be recovered from the pharynx prior to the onset of the symptoms of renal damage but cannot be isolated from the kidney at any stage of the disease. Nevertheless, during the active stage of acute nephritis, the sera of nephritic patients show a rising titer of antistreptolysin and other antibodies against products of Group A streptococci.[2] These observations indicate that glomerulonephritis follows hemolytic streptococcal infection at a distant site and that during the disease the influence of the streptococcus is measurable primarily by circulating antibody.

Attempts to produce acute glomerulonephritis in mice, rats, rabbits, dogs, goats, and monkeys by establishing an infection with various strains of hemolytic streptococci or by injecting streptococcal products have been largely unsuccessful.[3-6] Different types of living or dead streptococci in combination with kidney have been injected into animals of the same species supplying the renal tissue. The few reports on the successful production of glomerulonephritis following any of these various procedures still lack confirmation. In contrast, typical acute nephritis, the nephrotic syndrome, and chronic nephritis can be consistently produced by immunologic methods. The injection of specific antibodies to the kidney evokes a disease which closely simulates human nephritis with respect to natural history and histopathology. It is our purpose to describe this type of nephritis, to present limited data concerning the mechanism of the disease, and to discuss its possible relationship to the pathogenesis of the human disease.

THE EXPERIMENTAL DISEASE

Nephritis can be produced by immunologic means as follows: kidney tissue from animal species "A," perfused free of blood, is injected intramuscularly or intraperitoneally as an antigen into an animal of species "B." After an appropriate interval in which the maximal antibody development may occur,

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animal "B" is bled. The serum from "B" produces nephritis with great regularity when injected intravenously into a new member of the original species "A." Proteinuria, cylindruria, hypertension, and nitrogen retention occur. Masugi[7,8] made a major contribution to this field when he kept his animals under prolonged observation, following a single injection of the antikidney serum, and found that the acute nephritis might become chronic. Months later, some of the animals which had survived the acute phase died from renal insufficiency.

In the great majority of experiments, the rat, the rabbit, and the dog have served as species "A," the animal in which nephritis develops. The rabbit, the chicken, and the duck have been used as species "B" to produce the nephrotoxic antibody. The antigens with which these latter animals have been injected and which have stimulated production of the nephrotoxic antibody are whole kidney, glomeruli, and placenta. These data are summarized in Table I.

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TABLE I. ANIMALS IN WHICH NEPHROTOXIC ANTIBODY HAS BEEN PRODUCED

ANIMALS PROVIDING ANTIGEN (SPECIES A)	NATURE OF ANTIGEN	ANIMALS PRODUCING NEPHROTOXIC SERUM (SPECIES B)		
		RABBIT	CHICKEN	DUCK
Rat	Kidney	+	NT	+
Rat	Glomeruli	+	NT	+
Rat	Placenta	+	NT	NT
Rabbit	Kidney	NT	NT	+
Dog	Kidney	+	+	NT
Dog	Glomeruli	+	NT	NT
Dog	Placenta	+	NT	NT

+ = The serum obtained after immunization produces nephritis in a member of the species supplying the antigen.
NT = Not tested.

The course of the nephritis produced in the rat, the rabbit, and the dog are similar in most respects. Furthermore, the renal lesions bear a close resemblance to one another. A composite picture will therefore be presented of nephrotoxic nephritis in the rat, rabbit, and dog, based on studies carried out in this laboratory. An outline of the minor variations of the nephritis in individual animal species, together with references to the literature, will be found in Table II.

Manifestations of the Disease.—The picture of the acute phase of nephrotoxic nephritis is essentially that seen in human acute glomerulonephritis. The onset is abrupt and is often characterized by edema, hypertension, and proteinuria, with hyaline, cellular, and granular casts and red blood cells in the urinary sediment. Nitrogen retention develops within the first few days and hypercholesterolemia often is found. The acute disease may be fatal within a week to a month (Case 5).

If the animal survives the acute episode, one of three courses ensues. (1) Renal function may be steadily impaired and the animal dies in uremia within 3 to 9 months. This unremitting downhill course has been seen only after a severe

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TABLE II. THE CHARACTERISTICS OF NEPHRITIS PRODUCED IN THE RAT, RABBIT, AND DOG BY SPECIES-SPECIFIC ANTIRENAL, ANTIGLOMERULAR, OR ANTIPLACENTAL SERUM

EXPERIMENTAL ANIMAL	ANTISERUM	LATENT PERIOD OF PROTEINURIA (DAYS)	URINARY FINDINGS		EDEMA	HYPERTENSION	NITROGEN RETENTION	HYPERCHOLESTEROLEMIA	DEATH IN ACUTE OR SUBACUTE PHASE	DEATH FROM CHRONIC NEPHRITIS	COMPLETE RECOVERY	REFERENCES
			PROTEIN CASTS	RED BLOOD CELLS								
Rat	RARKS 0.3-2.4 ml.	0	+ +	0 or ±	+ or ++	+	+	+ or ++	+	+	+	7, 9, 10
	DARKS 0.3-1.6 ml.	0–21	+ +	0 or ±	± or +	+	+	+ or ++	+	+	+	10a, 11
	RARGS 1.0-1.5 ml.	0–20	+ +	0 or +	?	?	+	?	?	?	?	12
	DARGS 0.35-1.5 ml.	0	+ +	?	+	?	+	+	?	+	?	12
	RARPS 1.5 ml.	0	+ +	0 or +	0 or +	0 or +	+	+	+	+	+	13
Rabbit	DARbKS 2.0-5.5 ml./Kg.	0–9	+ +	+	0 or +	+	+	0 or +	+	+	+	8, 12, 14, 15, 16
Dog	RADKS 2.5-4.0 ml./Kg.	0	+ +	+	0 or +	+	+	0 or +	+	+	+	17, 18, 19
	CADKS ? ml./Kg.	6–10	+ +	+	0 or +	0	+	?	0	+	+	20
	RADGS 1.45-2.0 ml./Kg.	0	+ +	+	0 or +	0	+	+	+	?	?	12
	RADPS 2.0–3.2 ml./Kg.	0	+ +	+	0 or +	+	+	0 or +	+	+	+	18, 19, 21

RARKS : Rabbit antirat-kidney serum.
DARKS : Duck antirat-kidney serum.
RARGS : Rabbit antirat-glomerular serum.
DARGS : Duck antirat-glomerular serum.
RARPS: Rabbit antirat-placenta serum.
DARbKS: Duck antirabbit-kidney serum.
RADKS: Rabbit antidog-kidney serum.
CADKS: Chicken antidog-kidney serum.
RADGS: Rabbit antidog-glomerular serum.
RADPS: Rabbit antidog-placenta serum.
?: Insufficient data.

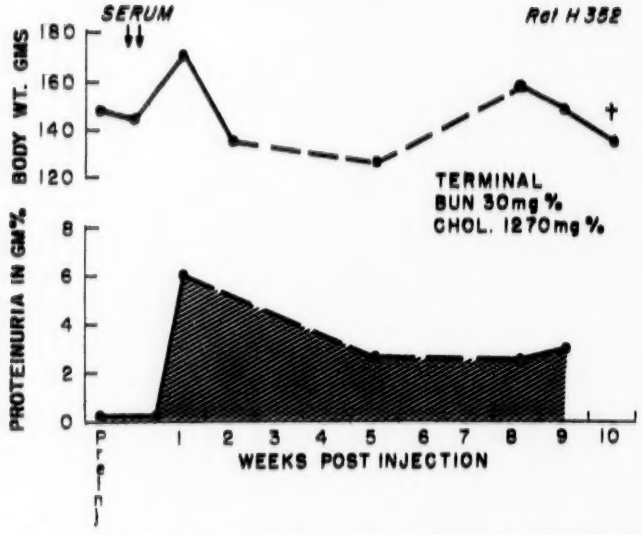

Chart I.—Rat H 352, injected with rabbit antirat-kidney serum, had an immediate massive proteinuria with a rapid gain in weight. A second period of increased weight associated with edema occurred in the eighth week. There were ascites and gross tissue edema at autopsy.

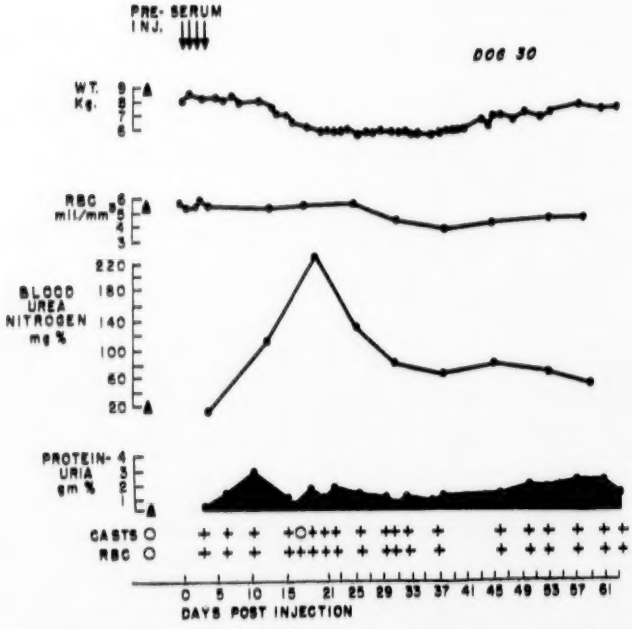

Chart II.—Dog 30, injected with rabbit antidog-placenta serum. The chart depicts the first 2 months during which the animal was acutely ill. (From Seegal, Bevans, and Hasson.[21] Courtesy Des Presses Imprimerie Medicale et Scientifique (S.A.) Brussels.)

acute disease. (2) About 10 per cent of animals with mild acute nephritis are cured completely. This has been confirmed by urinary and histopathologic examination as long as one year after the onset. (3) The more usual course is for the blood pressure and blood urea nitrogen to return to normal limits, while protein, casts, and red blood cells persist in the urine. In some rats the urine also is normal for a period, but proteinuria reappears in 2 to 7 months and nitrogen retention eventually recurs. Such animals with chronic nephritis may survive for years and finally succumb to renal insufficiency (Case 7 and Charts II and III). The majority of this group, however, die of other causes (age, infection). The pathologic lesions of chronic glomerulonephritis are present in all.

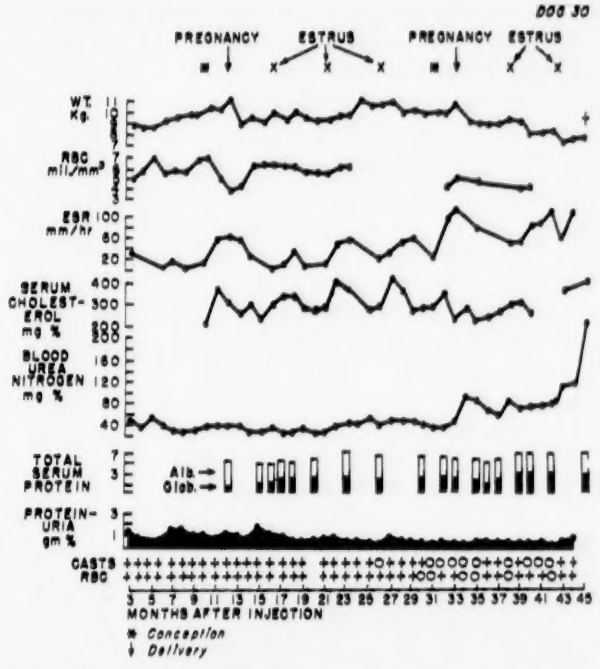

Chart III.—Dog 30 (continued). Observations from the third to the forty-fifth month following the injection of the antiplacenta serum. The animal was sacrificed when dying in uremia forty-four months after the onset of nephritis. (From Seegal, Bevans, and Hasson.[21] Courtesy Des Presses Imprimerie Medicale et Scientifique (S.A.) Brussels.)

A nephrotic syndrome characterized by massive edema and proteinuria, hypercholesterolemia, and hypoalbuminemia is often seen in the rat, particularly within the first week following the injection of very potent nephrotoxic serum. If the animal survives this episode, it develops a nonedematous phase of chronic nephritis which is usually fatal within a few months; the nephrotic syndrome may recur during this phase (Case 1 and Chart I).

The onset of nephritis customarily follows immediately upon the injection of nephrotoxic serum when this is prepared in rabbits. In contrast, pools of nephrotoxic serum obtained by immunizing the duck or chicken with the kidney of the rat, rabbit, or dog often produce a nephritis which is apparent only after a latent period of several days (Case 2). Once established, the course of the

disease and the renal lesions are comparable to those of the nephritis which occurs immediately upon injection of the antiserum. A possible explanation for the latent period will be discussed later.

Pathologic Findings.—

Acute nephritis: The kidneys are pale and swollen. The capsules are tense; the cortical striations are indistinct. After the third day, punctate hemorrhages may occur throughout the cortices.

The first renal lesion recognizable by routine microscopy is swelling of the glomerular basement membrane, which presents a hazy outline most effectively demonstrated by the periodic acid Schiff (PAS) stain. This is followed by the appearance of fibrin and hyaline thrombi occluding the capillaries and by partial or complete necrosis of the glomerular tufts. Bizarre giant cells formed by coalescence of the glomerular epithelial cells appear in the damaged tuft. Fibrin is seen in the capsular space and red blood cells are also present in the dog and rabbit, but seldom in the rat. Concomitantly, there is an infiltration of the glomeruli with leukocytes, predominantly lymphocytes, though polymorphonuclear cells and histiocytes can also be identified. Numbers of mitotic figures are seen in the glomerular cells, indicating proliferation of the cellular components, presumably epithelial cells. Varying degrees of swelling and desquamation of the lining cells of Bowman's capsule occur and delicate adhesions form between the tufts and capsule. Periglomerular cellular infiltration of polymorphonuclear cells, lymphocytes, and histiocytes are, in general, proportional to the severity of the glomerular lesion (Cases 3, 4, and 5 and Figs. 2-4).

Tubular damage is usually less pronounced than that encountered in the glomeruli. The basement membrane remains intact and well defined. The epithelial cells are swollen and often desquamated, so that they fill the lumen. Coagulum is abundant and casts can be seen as early as the second day. In the first few days these are hyaline or granular and become more numerous over the acute period. In the rabbit and dog red blood cell casts are also seen, but in the rat they are exceedingly rare. Hemosiderin and cellular casts appear later. Hyaline droplet degeneration and hemosiderin granules are present in the epithelial cells. Frequently, abnormal numbers of mitotic figures are observed, indicating attempts at repair of the damaged lining cells. Dilatation of the tubule occurs with the appearance of casts.

The interstitial tissue is edematous. Often a hyaline-like material which stains with PAS rims a severely damaged glomerulus. Lymphocytes, histiocytes, plasma cells, and polymorphonuclear cells are diffusely scattered throughout the interstitial tissue and focal collections of these cells are present about blood vessels and glomeruli.

In animals succumbing to the disease within the first 10 days, an occasional afferent arteriole to a necrotic glomerulus has a necrotic wall.

As the disease progresses beyond the fourteenth day, less and less exudation is apparent, and proliferation becomes the dominant tissue reaction. The necrotic tufts either disappear or are invaded by proliferating glomerular cells, most of which are probably of epithelial origin. The epithelial cells of Bowman's capsule also proliferate and the delicate adhesions of the earlier phase become thicker.

Subacute nephritis: The period between 30 and 60 days after onset has been arbitrarily designated as the subacute phase of the disease. The kidneys are large, pale, and often have finely granular surfaces. No fresh exudation is seen in the glomeruli, and the hazy basement membranes and capsules of the acute disease are converted to thick, well-defined structures. Fibrin thrombi are far less numerous in the glomerular tufts and some have a hyaline appearance. The adhesions between glomeruli and capsules are often thick and crescent formation is prominent. Tubular changes are commensurate with the glomerular damage; many are atrophic, others are dilated and contain hyaline, granular, and cellular casts. The epithelium lining the convoluted tubules varies from flat to tall; the tall epithelium often shows the hyaline droplet degeneration as well as the hemosiderin granules seen in the acute phase. Mitotic figures in the epithelial cells can be found frequently. The basement membranes of the tubules are irregularly thickened. The interstitial tissue increases in proportion to the atrophy of the tubules and is infiltrated with lymphocytes and histiocytes (Case 1 and Fig. 1).

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Chronic nephritis: In the chronic phase of the disease, the kidneys of experimental animals dying of nephritis from two months to several years after onset are usually larger than normal, in contrast to the contracted kidneys of human beings dying with chronic glomerulonephritis. The large kidneys are pale with finely pitted surfaces. The cortices are not reduced but the striations are indistinct. This difference from the human being may be a function of time, since one dog which died in uremia 3¾ years after injection had kidneys less than half the normal size (Case 7 and Fig. 6).

Microscopically, the glomerular lesions which affect almost every glomerulus show no fresh exudative changes. The glomeruli are often obliterated and can be recognized as fibrous balls containing varying amounts of hyaline deposit, which stains positively for mucopolysaccharides and lipid. Foam cells are occasionally present. The basement membranes become progressively thicker. The tubules show increasing atrophy or dilatation and the casts usually diminish in number except in the collecting ducts. The majority of casts are hyaline. Lipid can be visualized in many of the tubular epithelial cells. The interstitial tissue is increased and the cellular infiltration is lymphocytic and histiocytic.

The foregoing description applies to animals with fatal nephritis. It must be emphasized again that all gradations of severity may be encountered. Many animals develop a nephritis, as measured by clinical tests, which apparently heals; others continue to show a mild proteinuria until sacrifice. In these two groups a wide difference in the severity and extent of kidney lesions may be observed, but there is a distinct correlation between the clinical and anatomic manifestations of the disease. Those that have healed clinically, i.e., have normal urinalyses and no nitrogen retention, may show a few damaged glomeruli or an occasional cast in a tubule, but the changes observed are probably within the limits of normal anatomic wear and tear. Those animals which die or are sacrificed while showing mild proteinuria but no nitrogen retention show more diffuse lesions with large numbers of altered glomeruli and areas of scarring. It is to be noted that in these animals there is almost complete restoration to normal of the tubular epithelium.

Rats often develop a nephrotic syndrome early in the course of their nephritis or as a terminal manifestation of the disease. The histologic lesions in these kidneys are indistinguishable from those of animals dying in the dry phase and are of maximal intensity (Case 1 and Fig. 1).

The pathology of the progressive lesion of cytotoxic nephritis suggests that the disease which begins as a necrotizing and exudative lesion is the result of a single insult. From the early exudative phase there develops a proliferative phase which then is directed toward repair and is principally manifested by fibrosis. This is the usual sequence of events following injury to any part of the body.

NEPHROTOXIC NEPHRITIS AND SERUM DISEASE IN THE RABBIT

The results of experiments on nephrotoxic nephritis in rats, dogs, and rabbits have been compared with results obtained by the injection of equal amounts of normal serum or other organ antisera from the same species of animal supplying the nephrotoxic antibody. These latter sera have not produced disease. However, heterologous normal sera or serum fractions can produce kidney lesions which resemble those of acute nephritis when given to the rabbit in very large volume (10 ml. per kilogram), and especially when injected repeatedly. This "serum nephritis," first described by Klinge,[22] has been studied by many investigators, including Rich,[23] Ehrich,[14] Hawn and Janeway,[24] and Germuth.[25] The method for producing it and the nature of the lesions suggest that this renal disease is part of the general allergic reaction of serum sickness and is due to a reaction between the injected foreign protein and the antibodies to this protein produced by the host.

It may be that the nephritis associated with serum disease is due to a mechanism similar to that which is responsible for the nephrotoxic nephritis occurring only after a latent period of several days. Kay[16] has presented evidence indicating that antibodies to the foreign serum carrying the nephrotoxic antibody may initiate the nephritis. If rabbits are exposed to x-radiation before the injection of duck antirabbit-kidney serum, antibodies are not produced to the duck foreign protein and nephritis does not develop. To explain the latent period of nephrotoxic nephritis in the rabbit, Kay has postulated that the duck antirabbit-kidney antibody is bound by the kidney of the rabbit but that an inflammatory response resulting in nephritis takes place only when the rabbit has produced antibody to the duck globulin. This newly formed antibody then reacts with its homologous antigen, duck globulin, bound to the rabbit kidney, and nephritis results. Simonsen[15] has reported that in mesenchymal cells of the kidneys of nephritic rabbits there is an increase in the numbers of cells displaying affinity for pyronin stain. Since such cells are thought to be active in antibody production, Simonsen suggests that the antibodies to the duck globulin may be produced locally in the kidney. Ortega and Mellors,[26] employing Coons' fluorescent technique,[27] have made observations which led them to the conclusion that in the nephritic animal both the foreign serum containing the nephrotoxic antibody and the antibodies produced to this are present in the glomeruli. Mellors and Ortega[26a] are applying the same experimental methods to a study of human nephritis. They find that human serum

globulin is localized in the damaged glomeruli and they suggest that "it is logical to think . . . that localized gamma globulins are at least in part antibodies against antigens that have localized in the prospective sites of the lesion."

It should be emphasized that Kay's theory is designed to explain the mechanism of the nephritis arising several days after the injection of the nephrotoxic serum and does not relate to the nephritis which has an immediate onset. In this latter case, the initial antigen-antibody reaction between the host's kidney and the injected specific antikidney serum is of such intensity that renal damage is produced immediately. It would appear from our experience[11,12] that only the injection of relatively weak duck nephrotoxic serum gives rise to the delayed nephritis (Cases 2, 3, and 4).

ANTIGEN RESPONSIBLE FOR NEPHROTOXIC ANTIBODY

The nature of the substance in kidney which elicits the nephritis-producing antibody has been investigated by a variety of techniques. Evidence is accumulating which implicates the glomerulus as the source of this antigen. Solomon and his associates[28] devised a method for squeezing out the glomeruli from rat kidney. The suspended glomeruli absorbed all the nephritis-producing antibodies from rabbit antirat-kidney serum, rendering it harmless to the rat. They concluded, therefore, that the effective antigen resided in the glomerulus. Both rat and dog glomeruli as prepared in this laboratory have stimulated the production of specific nephrotoxic sera (Cases 3 and 6, and Figs. 2 and 5). Krackower and his co-workers[29] have further analyzed the source of the essential antigen by subjecting dog glomeruli to sonic disintegration. A fraction was obtained from the disrupted cells which, on the basis of morphology and staining reactions, appeared to be basement membrane. Only one-thirtieth as much of this material was required to produce nephrotoxic serum as was required when other portions of the glomerular residue were used as antigen to stimulate the production of nephrotoxic antibody.

The glomerulus, as the source of the antigen giving rise to nephrotoxic antibody, has been further implicated by a technique which tags the kidney antibody in order to follow its distribution in the body. Two means of labeling the antibody have been employed, with comparable results. Eisen, Sherman, and Pressman[30] have immunized rabbits with rat kidney, have separated the antibody from the serum, and have tagged it with radioactive iodine or sulfur. After the labeled antibody was injected into rats, its distribution in the body was followed by sacrificing the animals and determining the radioactivity of the total organs and by making radioautographs of the tissue sections. Their data demonstrated that antikidney serum localizes in the glomeruli.

Cruickshank and Hill[31] also have labeled both rabbit antirat-kidney and antirat-glomerular sera, using fluorescein isocyanate, according to the technique of Coons.[27] Thin slices of fresh normal rat kidney are cut and the antiserum, coupled with fluorescein, is applied. The areas which bind the antibody will fluoresce when examined under the microscope in ultraviolet light. The basement membranes of both glomeruli and tubules are found to bind antibody when antikidney serum is employed. However, the antirat-glomerular anti-

body is seen predominantly in the glomerular basement membrane. This antibody localized also in the basement membrane of the placenta. By utilizing the same techniques, we have found that, conversely, tagged rabbit antirat placenta antibody localizes in the basement membranes of rat glomeruli.[12]

PHYSIOLOGIC STUDIES IN EXPERIMENTAL NEPHRITIS

The study of experimental nephrotoxic nephritis has been concerned primarily with the natural history of the disease, the accompanying renal lesions, and the immunologic factors which are responsible for producing the syndrome. However, nephritis has been produced in some instances in order to investigate such matters as renal filtration,[20] factors which modify nephritis, or associated extrarenal disturbances.

The electron microscope has been used by Piel and her associates[32] to study changes in the kidney demonstrable in one hour following injection of antikidney serum. At this early period, osmophilic material may line the foot processes of the glomerular epithelial cells and obliterate all but narrow channels between the feet. This phase of the renal lesion corresponds in time with the early but brief period of anuria described by Lipmann.[33]

The effect of x-radiation in preventing the development of nephritis in the rabbit, as reported by Kay,[16] has been mentioned. Spühler and his co-workers[34] have found that cortisone reduced or prevented rabbit nephritis. However, when cortisone was injected into rats, nephritis produced either by rabbit or duck antirat-kidney serum was neither prevented nor reduced in severity.[35,36] Knowlton, Loeb, and Stoerk[37,38] have studied the effect of desoxycorticosterone acetate in nephritic rats. This steroid intensified both the renal lesions and the hypertension. Cortisone also intensified the hypertension accompanying nephrotoxic nephritis in the rat, although it did not modify the kidney lesions.[35]

Lange has studied the serum complement levels in human and experimental nephritis and in each case correlated the decrease of serum complement with the onset of the nephritis. Wenk and Lange[39] have perfused isolated rat kidneys with small amounts of rabbit antirat-kidney serum and have demonstrated that complement is removed from the perfusate under these conditions. Duck antirat-kidney serum used in a similar preparation failed to remove the complement. They concluded from these experiments that the failure of duck antirat-kidney serum to bind complement in the presence of rat kidney was related to the failure of this serum to produce an immediate nephritis. When the rat developed antibodies to the duck protein, complement decreased and nephritis occurred. It should be recalled, however, that a high titered duck antirat-kidney serum produces an immediate nephritis in rats. This fact is difficult to reconcile with the theory proposed by Lange.

Rats receiving antikidney sera together with desoxycorticosterone and high salt and fat diets have been reported to develop atheromatous lesions, especially of the coronary vessels.[40] Both the nephritis and the steroid were necessary to induce the vessel lesions in the rat, an animal normally resistant to atherosclerosis. The authors of this review have often found medial disease of the aorta and larger arteries and necrotizing lesions of the visceral vessels

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in the terminal stages of chronic nephritis in the rat. In our experience, the addition of cholesterol to the diets of nephritic rats treated with DOCA induced lipid infiltration about sites of injury in the vessel walls.

EXPERIMENTAL NEPHRITIS AND THE HUMAN DISEASE

It may well be asked what possible relationship can exist between nephrotoxic nephritis produced by the injection of specific antikidney serum and the human disease which follows a hemolytic streptococcus infection. The similarities in the clinical course and the renal lesions in the human and experimental disease have been described. Is there any way in which the mechanism of the two diseases can be related? There is no answer that has been put to the experimental test. There is, however, an hypothesis presented by Kay[16] and based upon his observations on the delayed type of nephritis which he studied in the rabbit. The hypothesis is that a soluble product of the streptococcus, escaping into the circulation from the local area of infection, lodges in the kidney. Here it behaves in a fashion analogous to the duck antikidney protein, which causes nephritis only after a latent period. Antibodies are formed by the human host to the streptococcus product or to a combination which it forms with the kidney. The antigen-antibody reaction, which then takes place in the kidney, is thought to be the cause of the nephritis. It would seem possible that the original union of kidney with antikidney antibody, or, in the case of human nephritis, with products of the hemolytic streptococcus might produce a "subclinical" kidney damage which would make the kidney more susceptible to the damaging effect of the second antigen-antibody reaction.

The newer methods of immunochemistry and histochemistry currently in use may make it possible to test this theory experimentally. By use of fluorescein-tagged antistreptococcus sera, the distribution of streptococcal antigens in the body can now be investigated. Furthermore, the development and localization in the body of the host of antibodies against streptococcal products can be studied by the use of fluorescein-tagged streptococcal antigens. Perhaps it is not too much to hope that information obtained from experimental nephritis may eventually throw some light on the mechanism of the human disease.

SUMMARY

1. Specific antikidney, antiglomerular, or antiplacenta serum, when injected in the rat or dog, produces acute glomerulonephritis, which may be fatal within a few days, may heal, or may progress to chronic nephritis resulting in death from renal failure months or years later. Duck antirabbit-kidney serum injected in rabbits produces a similar result.

2. The clinical course and pathologic lesions of this experimental disease resemble those of human nephritis.

3. In the rat, high-titered specific antisera may produce a nephrotic syndrome characterized by edema, hypercholesterolemia, hypoproteinemia, and massive proteinuria.

4. Between the clinical picture of acute nephritis and the onset of chronic nephritis in the rat, there may be an interval of several months during which time the animal appears normal.

5. Nephritis produced in rats, rabbits, or dogs by the injection of specific duck or chicken antikidney serum often has a latent period of several days.

6. Evidence has been presented that, at least in the rabbit, the onset of nephritis after a latent period is the result of a reaction between the injected antikidney foreign protein (fowl gamma globulin) attached to kidney parenchyma and the antibodies produced by the rabbit to this antigen.

7. The lesions of delayed nephritis in the rabbit, rat, or dog are similar to those which occur in nephritis with no latent period.

8. Evidence has been developed from chemical and histochemical studies of the glomerulus of the dog and rat which indicates that the basement membrane of the glomerulus may be the source of the antigen inciting production of the nephrotoxic antibody.

9. The new immunologic and histochemical techniques which have been used in the study of experimental nephrotoxic nephritis may in the future give data on the mechanism of human nephritis.

APPENDIX

The various manifestations of nephritis in the rat, rabbit, and dog as exemplified in individual animals is illustrated by the following series of case histories.

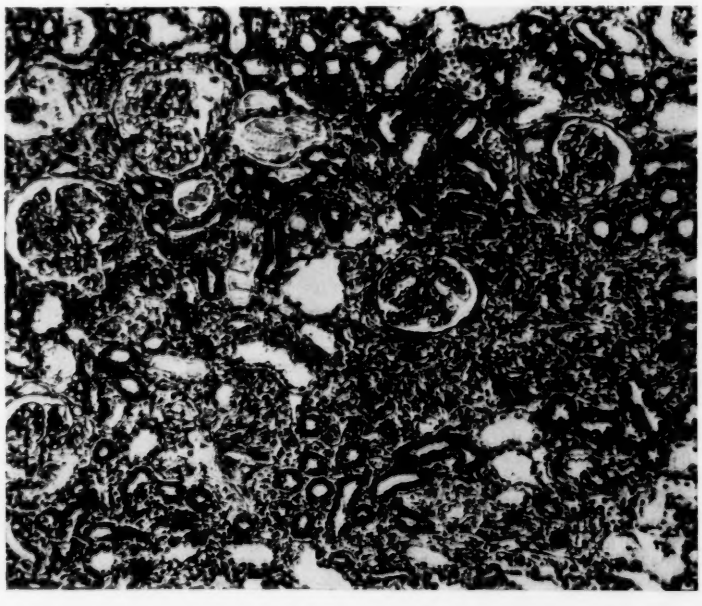

Fig. 1.—Rat H 352. Late subacute nephritis 70 days after the intravenous injection of 0.9 ml. of rabbit antirat-kidney serum. The glomeruli are severely damaged and are adherent to the capsule. The tubules are distorted and some contain hyaline casts. The interstitial tissue is increased and heavily infiltrated with lymphocytes and histiocytes. (Hematoxylin and eosin stain ×160.)

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CASE 1.—This rat, H-352, illustrates the nephrotic syndrome which developed during acute nephritis and again 8 weeks later when the animal might be considered in the subacute stage. The animal was a Long-Evans female 86 days of age when injected intravenously with a total of 0.9 ml. (3.6 ml. per kilogram) of rabbit antirat-kidney serum pool 465 on 2 successive days. Chart I shows the sharp rise in body weight and the massive output of protein in the urine which are typical of the nephrotic syndrome in the rat. Within two weeks the body weight fell to less than the initial value. A second rise in body weight, with gross edema, occurred shortly before the animal was etherized and exsanguinated. The terminal cholesterol was 1,270 mg. per cent and the blood urea nitrogen 30 mg. per cent. At autopsy, 5 ml. of fluid was found in the peritoneal cavity. The kidneys were large, pale, and granular.

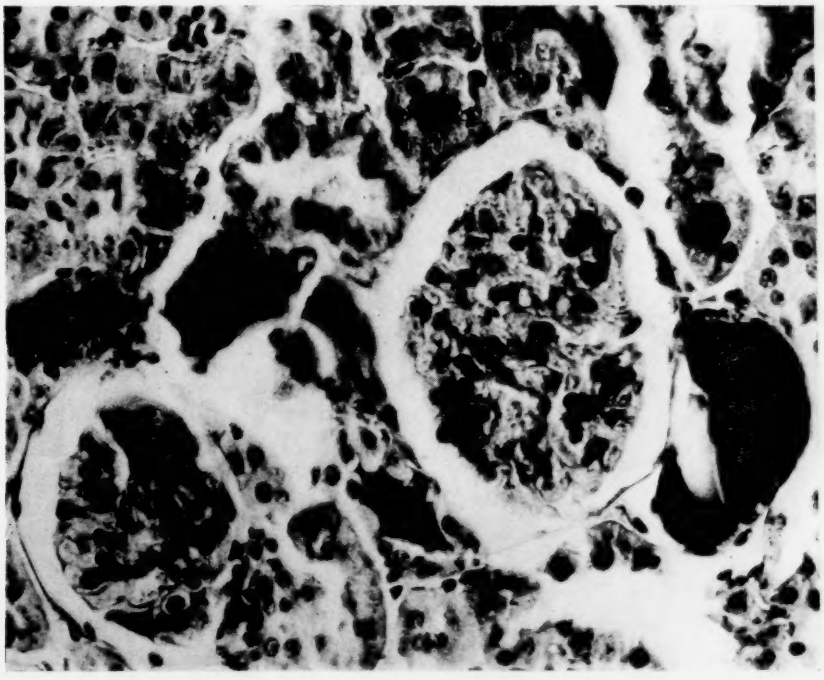

Fig. 2.—Rat SDB 515. Early lesions of acute glomerulonephritis 2 days after intravenous injection of 0.35 ml. duck antirat-glomerular serum. The basement membranes of the tufts are swollen and hazy. A few polymorphonuclear cells and lymphocytes infiltrate the tufts. Hyaline casts are present in the tubules. (PAS stain ×480.)

On microscopic examination almost every glomerulus was severely damaged (Fig. 1). Some were obliterated by a hyaline material which contained a few foam cells and pyknotic nuclei. The majority showed extensive adhesions to the capsules of Bowman, which were thickened both by hyaline deposits and fibrous tissue proliferation. In the better-preserved glomeruli, numerous foam cells stained for lipid in "Oil Red O" preparations. The hyaline material was positive for lipid and for mucopolysaccharides in PAS stains. The tubules were dilated or atrophic and the tubular epithelium contained varying amounts of fat. Hyaline casts were numerous. There was a dense infiltration of lymphocytes throughout the interstitial tissue.

CASE 2.—Some lots of nephrotoxic serum obtained from ducks result in nephritis only after a latent period of several days following injection. The latent period, in our experience, has been the result of injecting relatively low-titered serum. Once the nephritis is established, its course and the renal lesions are similar to those seen in the immediate disease. This is illustrated by rat SDB 9, a Sprague-Dawley male 106 days old when injected intravenously over 3 successive days

with a total of 1.6 ml. (4.5 ml. per kilogram) of duck antirat-kidney serum, pool I. There was no abnormal proteinuria until 11 days after the last injection. During the following 71 days the proteinuria varied from 0.7 to 2.2 Gm. per cent. On the eighty-fifth day of the experiment the animal was etherized and exsanguinated. The terminal blood urea nitrogen was 48 mg. per cent and the serum cholesterol 283 mg. per cent.

At autopsy the kidneys were finely granular. On microscopic examination most of the glomeruli proved to be partially or completed obliterated or atrophic. Hyaline deposits and fibrous tissue proliferation were seen in the tufts and in the capsule. Many tubules were atrophic and others greatly dilated and the lumina filled with hyaline casts. There was a diffuse infiltration of lymphocytes in the abundant interstitial tissue.

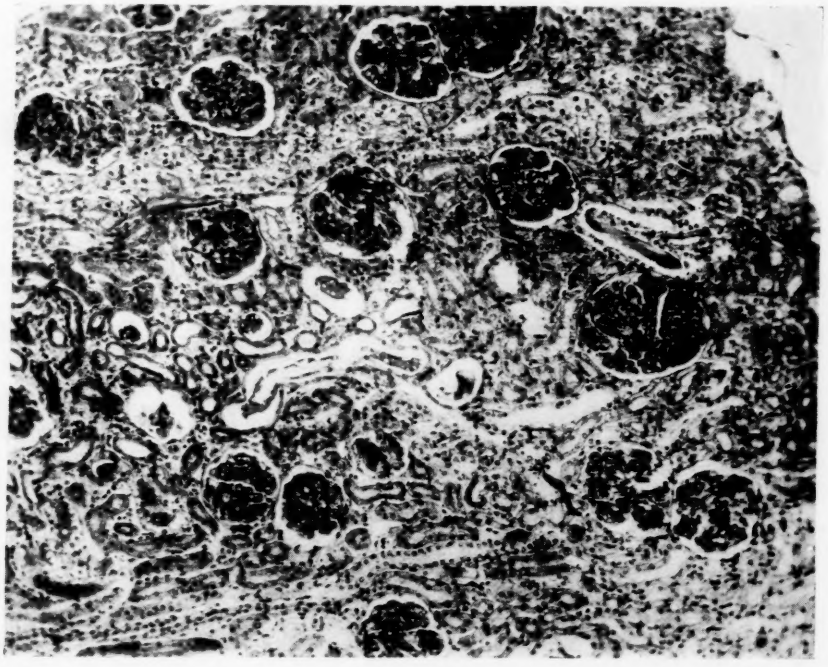

Fig. 3.—Rabbit 182. Severe nephritis 6 days after the intravenous injection of 3 ml. per kilogram of duck antirabbit-kidney serum. Note necrosis of the glomerular tufts, some of which are adherent to the capsules. Numerous casts are seen in dilated tubules. Elsewhere, the tubular epithelium is swollen and contains hyaline droplets. Polymorphonuclear cells, lymphocytes, and histiocytes infiltrate the interstitial tissue. (PAS stain ×100.)

CASE 3.—Glomeruli squeezed out of the kidney cortex and washed almost entirely free of tubular debris readily stimulate the production of the nephrotoxic antibody. An early lesion of nephritis in the rat following the injection of duck antirat-glomerular serum is illustrated by rat SDB 515, a Sprague-Dawley female 71 days of age when injected intravenously on 2 successive days with a total of 0.35 ml. (1.7 ml. per kilogram) of duck pool V. Proteinuria of 4.5 Gm. per cent was noted the day after the last injection. The animal was sacrificed the following day at which time the blood urea nitrogen was 15 mg. per cent and the blood cholesterol 89 mg. per cent. Approximately 3 ml. of free fluid was found in the abdominal cavity. The kidneys were not grossly abnormal. On microscopic examination the glomerular basement membranes were swollen and hazy (Fig. 2). Small numbers of fibrin thrombi occluded the glomerular capillary loops. Many of the glomerular nuclei appeared large and hyperchromic. Occasional thin fibrin strands stretched across the space from the tuft to Bowman's capsule A few lymphocytes and polymorphonuclear

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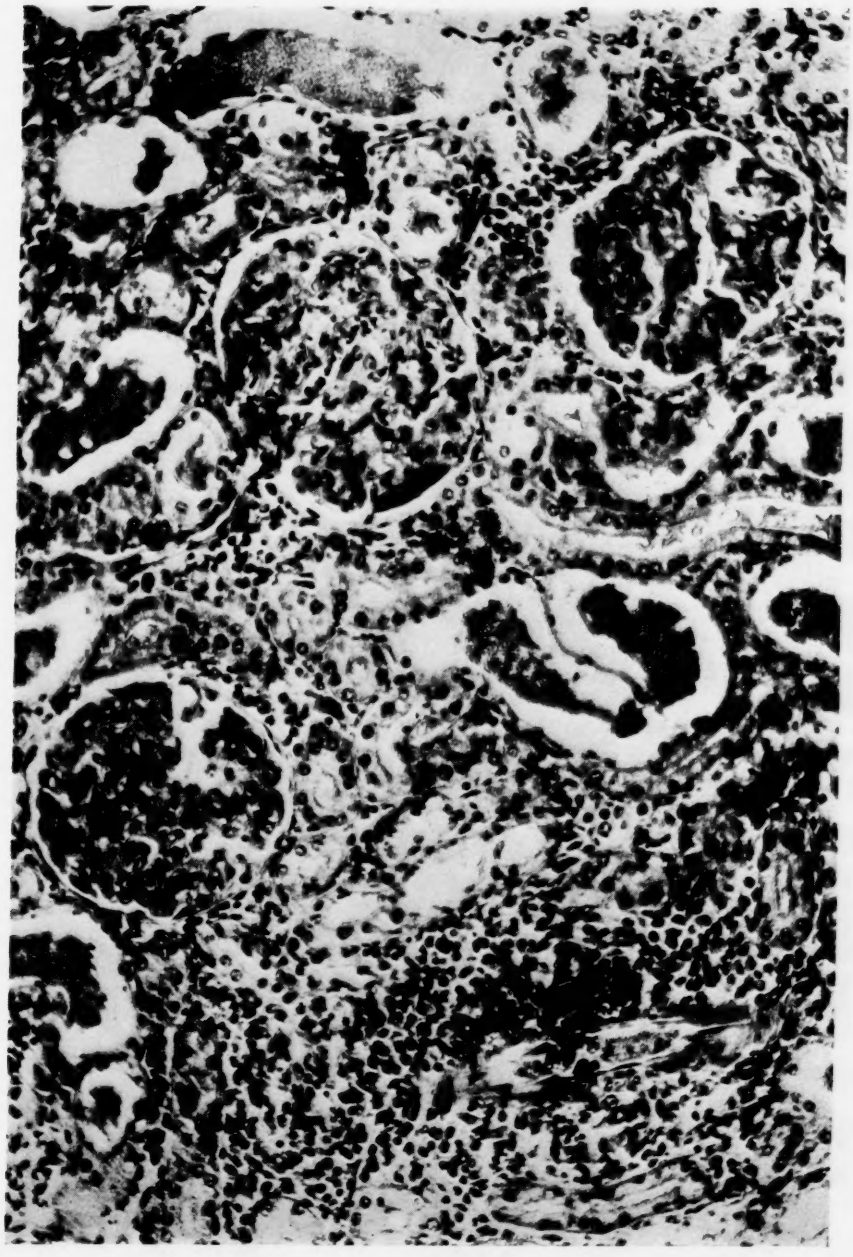

Fig. 4.—Dog M 7. Acute glomerulonephritis 9 days after the intravenous injection of 3 ml. per kilogram of antidog-placenta serum. The glomerular basement membranes are swollen. Polymorphonuclear leukocytes, lymphocytes, and plasma cells are present in the tufts and in the interstitial tissue. The tubular epithelium is swollen and, in some areas, desquamated. Casts are seen in the lumina of dilated tubules. Necrosis of the wall of a small artery and cellular reaction appear at the bottom. Similar lesions in the arterioles are indicated by the black streaks near the glomerulus on the upper left. (Hematoxylin and eosin stain × 300.) (From Bevans, Seegal, and Kaplan.[19] Courtesy J. Exper. Med.)

cells were seen both in the glomeruli and about the capsule. Within the tubules there were hyaline casts and large amounts of coagulum. The epithelium was swollen so that many of the lumina appeared occluded. A few epithelial cells desquamated into the lumina. Hyaline droplet degeneration was slight. The interstitial tissue was edematous and infiltrated with lymphocytes and polymorphonuclear cells. No vascular lesions were seen.

CASE 4.—The reports in the literature of nephritis in rabbits produced by duck antirabbit-kidney serum almost invariably state that there is a latent period of several days before the manifestation of renal damage. The one pool of duck antirabbit-kidney serum prepared in this laboratory has induced immediate proteinuria with casts and red blood cells in the urinary sediment and marked nitrogen retention. The case history of the Dutch rabbit 182 presents the course of the disease in an animal killed on the sixth day after injection. This animal was injected intravenously on 3 successive days with a total of 4.3 ml. (3 ml. per kilogram) of duck antirabbit-kidney serum pool I. This serum, like all others used to produce experimental nephritis, had been absorbed with specific rabbit red blood cells to remove all hemagglutinins. Proteinuria of 0.2 Gm. per cent was present before the last injection and increased during the next 6 days to 1.4 Gm. per cent. Granular cellular and hyaline casts as well as occasional red blood cells were seen in the urinary sediment from the second day on. The blood urea nitrogen was 43 mg. per cent on the sixth day when the animal was sacrificed. At autopsy, about 3 ml. of clear fluid was found in the peritoneal and pleural cavities. The kidneys were pale and moist.

Microscopically, almost every glomerulus was severely damaged, as may be seen in Fig. 3. There was necrosis of the tufts with masses of nuclear debris in a brilliantly eosinophilic fibrinoid material. Fibrin thrombi occluded the capillaries. The basement membranes of the glomeruli were swollen and hazy in appearance. Polymorphonuclear cells and lymphocytes infiltrated the tufts and were present in the capsular space and about the capsule of Bowman. Gaint cells and mitotic figures were seen within the glomeruli. The epithelium of the capsule was often detached and cells were seen within the capsular space, while that which remained attached was swollen and showed early proliferation. Delicate adhesions were seen between the tufts and capsule. Numerous hyaline, red blood cell and granular casts were present in the tubules, many of which were dilated. The tubular epithelium, which contained small vacuoles, was swollen to such a degree that many of the lumina appear occluded. The interstitial tissue was heavily and diffusely infiltrated with polymorphonuclear cells and lymphocytes. No arterial or arteriolar lesions were seen.

The dog presents a picture of both acute and chronic nephritis which is strikingly similar to the human disease. The course of the disease in 3 dogs, one dying of acute nephritis in 9 days, one sacrificed after 5 months of nephritis, and one dying with chronic nephritis in 3 years and 9 months, illustrates the features of nephritis in this animal.

CASE 5.—Dog M 7, a female mongrel of unknown age weighing 9.3 Kg., was injected intravenously on 3 successive days with a total of 3 ml. per kilogram of rabbit antidog-placenta serum. Protein, casts, and red blood cells were found in the urine on the first day following injection, and there was edema of the face and extremities, vomiting, bloody diarrhea, and hypertension from the third until the ninth day, when the animal was moribund and was killed with ether anesthesia. The total serum cholesterol at death was 91 mg. per cent and the blood urea nitrogen 196 mg. per cent.

At autopsy, the kidneys-appear finely pitted and the cortex was studded with pinpoint hemorrhages. Microscopically, almost every glomerulus was severely damaged (Fig. 4). Some tufts were necrotic; others showed proliferation of both epithelial and endothelial cells. There were fibrin thrombi in the glomerular capillaries and red blood cells and fibrinoid material in the capsular space. Delicate adhesions were present between the tufts and capsule. The capsular epithelium was swollen and often desquamated. Hyaline droplet degeneration was prominent. Infiltration of polymorphonuclear cells, lymphocytes, histiocytes, and plasma cells tended to have a peri-

glomerular and perivascular distribution and were also present within the glomerular tufts. There was a necrotizing arteritis of the stomach and also of a small vessel in the kidney, as may be seen in Fig. 4.

CASE 6.—Dog N 11, a 6-month-old male beagle weighing 9 Kg., was sacrificed while showing evidence of chronic nephritis. This animal was injected intravenously with a total of 1.45 ml. per kilogram of rabbit antidog-glomerular serum on 2 successive days. On the second day of injection, the urine contained 1.9 Gm. per cent of protein and granular and red blood cell casts. During the first week, the proteinuria increased to 2.4 Gm. per cent and the blood urea nitrogen rose to 41 mg. per cent. The serum albumin-globulin ratio was reversed (2.1/2.8 Gm. per cent), and the erythrocyte sedimentation rate was 60 mm. in one hour. Hypertension was not present in this dog. For the following 4 months, proteinuria with casts and red blood cells in the urinary sediment persisted. Blood urea nitrogen fell to within the upper limits of normal.

The dog was sacrificed by pentobarbital anesthesia 5 months after injection.

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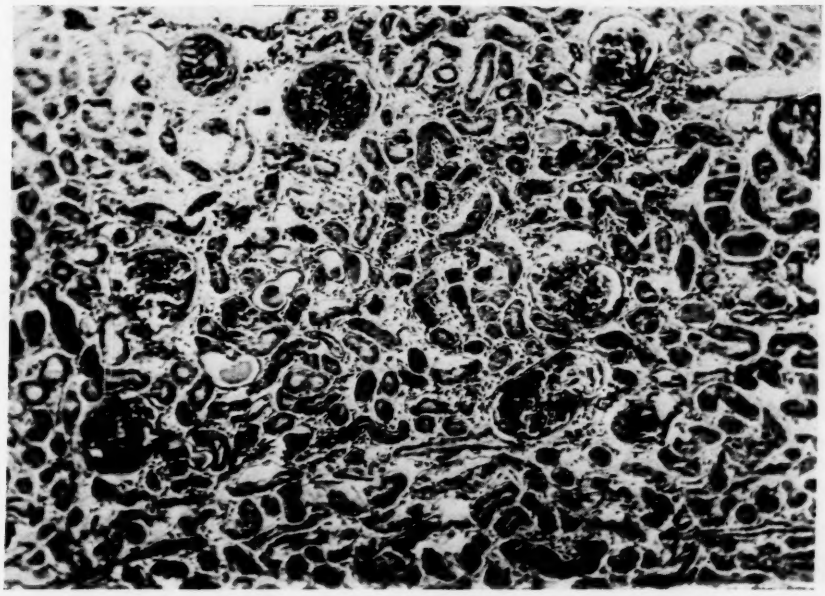

Fig. 5.—Dog N 11. Chronic nephritis 5 months after the intravenous injection of 1.45 ml. per kilogram of antiglomerular serum. The glomeruli are severely damaged. Many obliterated tufts are adherent to the capsule. The tubules contain numerous casts. The interstitial fibrous tissue is increased and infiltrated with lymphocytes and histiocytes. (PAS stain ×100.)

The kidneys were large and pale and the surfaces finely pitted. The cortical striations were indistinct. All glomeruli were severely damaged (Fig. 5); some were obliterated; others had capillary beds partially occluded by hyaline deposits. Many were adherent to the capsule by fibrous adhesions. Bowman's capsules also were thickened by fibrous tissue. The tubules contained numerous hyaline casts and the epithelium varied from flat to high columnar. Occasional hemosiderin deposits were seen within the epithelial cells. The interstitial tissue was increased and infiltrated with lymphocytes and histiocytes.

CASE 7.—When a dog survives the acute stage, it usually develops chronic nephritis which may run a very protracted course. This is illustrated by Dog 30, a female beagle aged 1½ years and weighing 8.2 Kg. when injected intravenously on 4 successive days with a total of 3.0 ml. per kilogram of rabbit antidog-placenta serum.

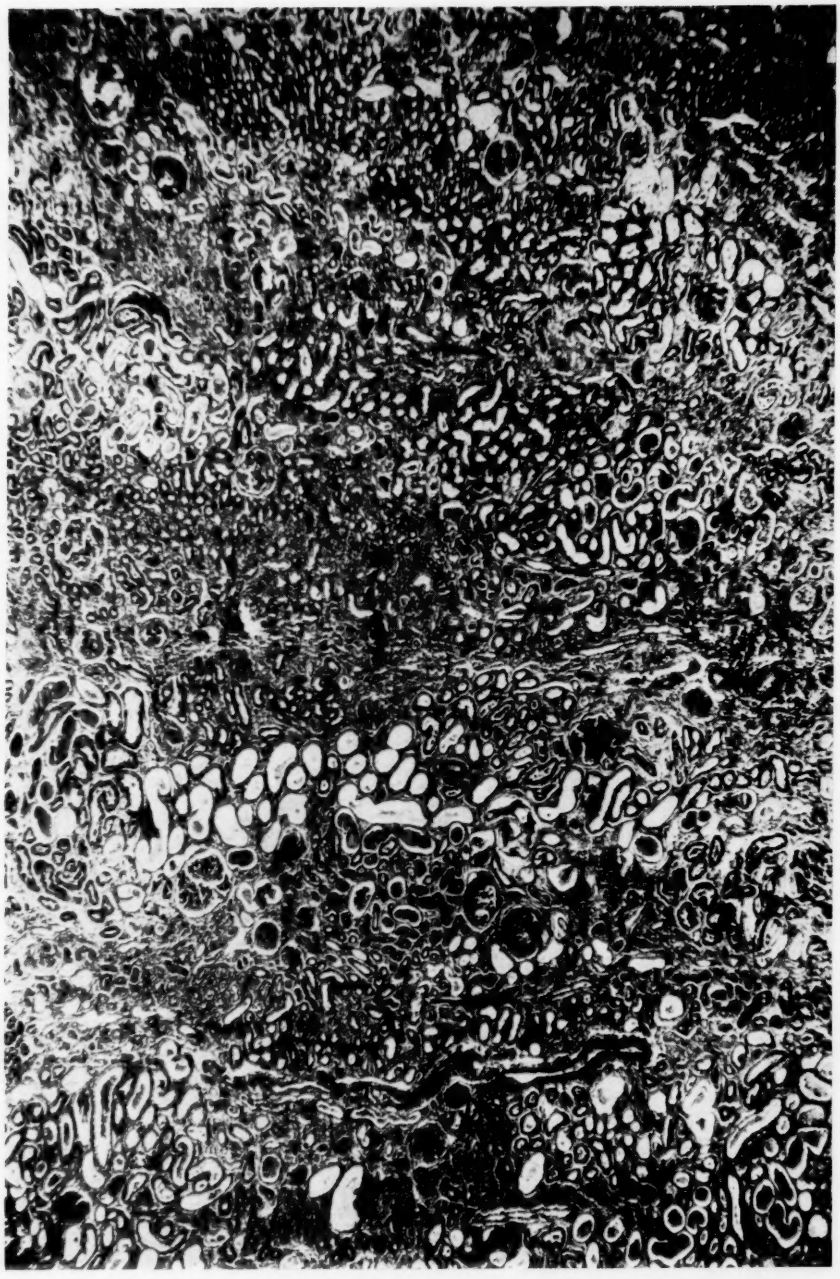

Fig. 6.—Dog 30. Chronic nephritis fatal 3 years and 8 months after intravenous injection of 3 ml. per kilogram of rabbit antidog-placenta serum. Low-power view showing scarring and distortion of the renal parenchyma. There are many severely damaged glomeruli in the field. In addition, atrophic tubules and dilated tubules containing casts are seen in the interstitial fibrous tissue. (Hematoxylin and eosin stain ×30.) (From Seegal, Bevans, and Hasson.[21] Courtesy Des Presses Imprimerie Medicale et Scientifique (S.A.) Brussels.)

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Charts II and III present the course of the nephritis, which terminated in renal insufficiency 3 years and 8 months following the injection of the rabbit antiserum. Fig. 2 covers the first 2 months, which were chararcterized by proteinuria with casts and red cells in the urinary sediment, a markedly elevated blood urea nitrogen, anemia, and loss of weight. There was facial edema, the gums were inflamed, and there were necrotic buccal plaques. During the following 2½ years (Chart III), the dog continued to excrete protein, casts and red cells in the urine and the blood urea nitrogen was usually slightly elevated. In the final year of life, the clinical course of the nephritis became more severe. The blood urea nitrogen was never below 50 mg. per cent. There was a persistent anemia and the erythrocyte sedimentation rate was constantly elevated. Serum globulin increased to 3 Gm. per cent. When the animal was moribund, it was killed with anesthesia.

At autopsy, the kidneys were pale and contracted. The surface was granular and the corticomedullary striations were distorted. Almost every glomerulus was damaged (Fig. 6); many were partially or completely hyalinized. There were adhesions of glomeruli to the capsule. Hyaline deposits in the glomerular capillaries stained positively for lipid and for mucopolysaccharides. Proliferation of glomerular and capsular epithelium was prominent. The interstitial fibrous tissue was increased and densely infiltrated with lymphocytes and histiocytes. Many tubules were obliterated; some were atrophic; others dilated. There were numerous hyaline, granular, and waxy casts, as well as anisotropic crystals resembling those of uric acid, within the lumina of the tubules.

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